II. Rationale for Intervention

1. Basic description of lipids and lipoproteins

Cholesterol is a fat-like substance (lipid) that is present in cell membranes and is a precursor of bile acids and steroid hormones. Cholesterol travels in the blood in distinct particles containing both lipid and proteins (lipoproteins). Three major classes of lipoproteins are found in the serum of a fasting individual: low density lipoproteins (LDL), high density lipoproteins (HDL), and very low density lipoproteins (VLDL). Another lipoprotein class, intermediate density lipoprotein (IDL), resides between VLDL and LDL; in clinical practice, IDL is included in the LDL measurement.

LDL cholesterol typically makes up 60–70 percent of the total serum cholesterol. It contains a single apolipoprotein, namely apo B-100 (apo B). LDL is the major atherogenic lipoprotein and has long been identified by NCEP as the primary target of cholesterol-lowering therapy. This focus on LDL has been strongly validated by recent clinical trials, which show the efficacy of LDL-lowering therapy for reducing risk for CHD.

HDL cholesterol normally makes up 20–30 percent of the total serum cholesterol. The major apolipoproteins of HDL are apo AI and apo AII. HDL-cholesterol levels are inversely correlated with risk for CHD. Some evidence indicates that HDL protects against the development of atherosclerosis, although a low HDL level often reflects the presence of other atherogenic factors.

The VLDL are triglyceride-rich lipoproteins, but contain 10–15 percent of the total serum cholesterol. The major apolipoproteins of VLDL are apo B 100, apo Cs (CI, CII, and CIII), and apo E. VLDL are produced by the liver and are precursors of LDL; some forms of VLDL, particularly VLDL remnants, appear to promote atherosclerosis, similar to LDL. VLDL remnants consist of partially degraded VLDL and are relatively enriched in cholesterol ester. Strictly speaking, IDL belongs to remnant lipoproteins although, in clinical practice, IDL is included in the LDL fraction.

A fourth class of lipoproteins, chylomicrons, are also triglyceride-rich lipoproteins; they are formed in the intestine from dietary fat and appear in the blood after a fat-containing meal. The apolipoproteins of chylomicrons are the same as for VLDL except that apo B-48 is present instead of apo B-100. Partially degraded chylomicrons, called chylomicron remnants, probably carry some atherogenic potential.

Although LDL receives primary attention for clinical management, growing evidence indicates that both VLDL and HDL play important roles in atherogenesis. In this report, therefore, VLDL and HDL receive consideration after LDL in the overall management of persons at risk for CHD.

2. LDL cholesterol as the primary target of therapy

ATP I and ATP II identified LDL as the primary target for cholesterol-lowering therapy, and ATP III continues this emphasis. This designation is based on a wide variety of observational

and experimental evidence amassed over several decades from animal, pathological, clinical, genetic, and different types of population studies. Many earlier studies measured only serum total cholesterol, although most of total cholesterol is contained in LDL. Thus, the robust relationship between total cholesterol and CHD found in epidemiological studies strongly implies that an elevated LDL is a powerful risk factor. Subsequent studies have shown that LDL is the most abundant and clearly evident atherogenic lipoprotein. The role of LDL in atherogenesis is confirmed by genetic disorders in which serum LDL cholesterol is markedly increased in the absence of other CHD risk factors. Notable examples of such genetic disorders are homozygous and heterozygous forms of familial hypercholesterolemia; in both, atherogenesis is markedly accelerated. Finally, a causal role for LDL has been corroborated by controlled clinical trials of LDL lowering; recent trials especially have revealed a striking reduction in incidence of CHD. Evidence for LDL being both a major cause of CHD and a primary target of therapy will be examined in some detail.

a. Serum LDL cholesterol as a major cause of CHD

The induction of hypercholesterolemia is a prerequisite for atherogenesis, and sometimes myocardial ischemia, in various experimental animals. In addition, certain species have hereditary forms of hypercholesterolemia and develop atherosclerosis spontaneously; a classical example is the WHHL rabbit, which carries the same molecular defect as human familial hypercholesterolemia. In contrast, low LDL-cholesterol levels are well tolerated. LDL cholesterol as low as 25–60 mg/dL is physiologically sufficient (Brown and Goldstein, 1986). Animal species that do not develop atherosclerosis generally have LDL-cholesterol levels below 80 mg/dL. The LDL-cholesterol concentration in the newborn infant is approximately 30 mg/dL, indicating that such low levels are safe. Moreover, persons who have extremely low levels of LDL throughout life due to familial hypobetalipoproteinemia have documented longevity (Glueck et al., 1976).

Epidemiological investigations of human populations incriminate high levels of LDL cholesterol as being atherogenic. In population studies, the serum total cholesterol is a good surrogate for LDL-cholesterol levels. The Framingham Heart Study (Wilson et al., 1998), the Multiple Risk Factor Intervention Trial (MRFIT) (Stamler et al., 1986), and the Lipid Research Clinics (LRC) trial (Lipid Research Clinics Program 1984a,b) found a direct relationship between levels of LDL cholesterol (or total cholesterol) and the rate of new-onset CHD in men and women who were initially free of CHD. The same relation holds for recurrent coronary events in people with established CHD (Rossouw et al., 1990; Pekkanen et al., 1990; Wong et al., 1991). Any LDL cholesterol above 100 mg/dL appears to be atherogenic. The prevalance of elevated levels in large part accounts for the near-universal development of coronary atherosclerosis in the United States and the high attendant risk for developing CHD over a lifetime—49 percent for men and 32 percent for women (Lloyd-Jones et al., 1999).

Studies across different populations reveal that those with higher cholesterol levels have more atherosclerosis and CHD than do those having lower levels (McGill 1968; Keys et al., 1980; 1984). People who migrate from regions where average serum cholesterol in the general population is low to areas with high cholesterol levels show increases in their cholesterol levels

as they acculturate. These higher levels in turn are accompanied by more CHD (Kagan et al., 1974; Toor et al., 1960).

The positive relationship between serum cholesterol levels and the development of first or subsequent attacks of CHD is observed over a broad range of LDL-cholesterol levels; the higher the level, the greater the risk (Stamler et al., 1986). Early prospective data suggested that the risk of CHD plateaued at lower cholesterol levels, but this apparent plateau has disappeared in larger studies (Stamler et al., 1986; Law et al., 1994b; Law 1999). Only in populations that maintain very low levels of serum cholesterol, e.g., total cholesterol <150 mg/dL (or LDL cholesterol <100 mg/dL) throughout life do we find a near-absence of clinical CHD (Keys et al., 1980; Grundy et al., 1990; People's Republic . . . 1992; Law et al., 1994a–c; Law 1999).

Atherosclerosis generally can first be identified by gross pathological examination of coronary arteries in adolescence or early adulthood (McGill et al., 1997; 1998; 2000). The subsequent rate of atherogenesis is proportional to the severity of ambient risk factors including serum cholesterol levels. Moreover, the cholesterol level in young adulthood predicts development of CHD later in life. In three prospective studies with long-term followup (Anderson et al., 1987; Klag et al., 1993; Stamler et al., 2000), detection of elevated serum cholesterol in early adulthood predicted an increased incidence of CHD in middle-age.

The power of elevated LDL to cause CHD is shown most clearly in persons with genetic forms of hypercholesterolemia (Brown and Goldstein, 1986). In these persons, advanced coronary atherosclerosis and premature CHD occur commonly even in the complete absence of other risk factors. These disorders provide the strongest evidence that LDL is a powerful atherogenic lipoprotein.

Since LDL-cholesterol levels <100 mg/dL throughout life are associated with a very low risk for CHD in populations, they can be called *optimal.* Even when LDL-cholesterol concentrations are *near optimal* (100–129 mg/dL), atherogenesis occurs; hence, such levels must also be called *above optimal.* At levels that are *borderline high* (130–159 mg/dL), atherogenesis proceeds at a significant rate, whereas at levels that are *high* (160–189 mg/dL) and *very high* ($\geq$190 mg/dL) it is markedly accelerated. These relationships are confirmed by the log-linear relationship between serum cholesterol levels and CHD risk observed in many populations (Law et al., 1994b; Law 1999).

The relation of elevated LDL cholesterol to the development of CHD must be viewed as a multi-step process beginning relatively early in life (Stary et al., 1992; 1994; 1995). The first stage of atherogenesis is the fatty streak, which consists largely of cholesterol-filled macrophages; most of the cholesterol in fatty streaks is derived from LDL cholesterol. The second stage consists of fibrous plaques in which a layer of scar tissue overlies a lipid-rich core. Other risk factors contribute to plaque growth at this phase. The third stage is represented by the development of unstable plaques that are prone to rupture and formation of luminal thrombosis. Plaque rupture (or erosion) is responsible for most acute coronary syndromes (myocardial infarction, unstable angina, and coronary death) (Libby 1995; Libby et al., 1998; Fuster et al., 1999; Theroux and Fuster, 1998). Elevated LDL cholesterol plays a role in the development of the mature coronary plaque, which is the substrate for the unstable plaque. Recent evidence also indicates that elevated LDL cholesterol contributes to plaque instability as well; conversely, LDL cholesterol

lowering stabilizes plaques and reduces the likelihood of acute coronary syndromes. Clinical intervention with LDL-lowering therapy in patients with advanced coronary atherosclerosis (short-term risk reduction) thus aims to stabilize plaques and to prevent acute coronary syndromes (Brown et al., 1995; Brown and Zhao, 2000). In contrast, LDL lowering earlier in life slows atherosclerotic plaque development, the foundation of the unstable plaque. This fact provides a rationale for long-term lowering of LDL cholesterol using both public-health and clinical approaches.

b. Serum LDL cholesterol as target of therapy

Notwithstanding this diverse evidence, the ultimate proof of the benefits of lowering LDL cholesterol is through clinical trial. A large number of clinical trials of cholesterol-lowering therapy have been carried out over the past four decades (Grundy 2000a). The history of cholesterol-lowering trials records one of the major advances in modern medicine (Grundy 2000a). The initial encouraging findings of earlier trials have recently been reinforced by the robust findings of a large number of studies, especially those using HMG CoA reductase inhibitors (statins). Clinical outcomes in terms of CHD incidence and CHD mortality are summarized in Table II.2–1 for pre-statin and statin trials in which LDL-cholesterol reduction was the major lipid response. The pre-statin trials provided strong evidence that CHD incidence is reduced by cholesterol-lowering therapy; statin trials extend the benefit to reduction of CHD mortality, and even to total mortality (see Section II.9).

Table II.2–1.* CHD Outcomes in Clinical Trials of LDL-Cholesterol-Lowering Therapy†

Intervention	No. trials	No. treated	Person-years	Mean cholesterol reduction (%)	CHD Incidence (% change)	CHD Mortality (% change)
Surgery	1	421	4,084	22	**-43**	-30
Sequestrants	3	1,992	14,491	9	**-21**	-32
Diet	6	1,200	6,356	11	**-24**	-21
Statins	12	17,405	89,123	20	**-30**	**-29**

* This table is adapted from the meta-analysis of Gordon 2000.

† Not included among these clinical trials are those employing fibrates, nicotinic acid, and hormones. The major actions of fibrates and nicotinic acid are on triglyceride and HDL, whereas hormone trials have effects beyond serum lipids.

Additional evidence of the benefit of LDL lowering is provided by study of coronary lesion architecture through coronary angiography. A summary of the evidence from different categories of angiographic trials reveals that LDL-lowering therapy produces favorable outcomes for coronary lesions, with a strong trend for a beneficial outcome for major coronary events (Table II.2–2).

Table II.2–2. Odds Ratios for Coronary Lesion Regression vs. Progression and for Cardiovascular Event Rates in Angiographic Trials of LDL-Lowering Therapy (Including Comparison with Placebo and Trials of Calcium Channel Blockers)

Trials	Coronary Lesion Regression vs. Progression Odds Ratio (Number >1 means greater regression than progression)	Cardiovascular Event Rates Odds Ratio (Number <1 means fewer events on therapy)
Statins	2.1 (1.6, 2.7)* (p<0.0001)(vs. placebo)† (p<0.0001)vs. calcium blocker)‡	0.67 (0.57, 0.80)* (p<0.0001)† (p=0.012)‡
Ileal Excluson (POSCH)	4.7 (2.5, 9.0)* (p<0.0001)† (p=0.002)‡	0.57 (0.41, 0.78)* (p<0.0005)† (p=0.0082)‡
Sequestrants	3.2 (0.9, 11.4)* NS† NS‡	0.41 (0.17, 1.00)* NS† NS‡
Lifestyle	10.7 (4.0, 29.0)* (p<0.0001)† (p=0.0004)‡	0.57 (0.23, 1.46)* NS† NS‡
Combination Therapy	3.0 (1.8, 5.1)* (p<0.0001)† (p=0.03)‡	0.54 (0.36, 0.81)* (p=0.0031)† (p=0.021)‡
Calcium Channel Blockers	1.0 (0.6, 1.4)* NS†	1.33 (0.94, 1.89)* NS†

* Confidence intervals.

† Statistical significance compared to placebo.

‡ Statistical significance compared to calcium channel blocker trials.

This table was modified from a recently published meta-analysis provided by G.B.J. Mancini (Holmes et al., 2000). In this analysis, to assess trends and to synthesize the results of disparate trials, the reported trial results were examined with respect to the main angiographic and clinical endpoints. Odds ratios were calculated comparing progression and regression as dichotomous responses, excluding mixed or no-change responses. Odds ratios also were calculated for reported events. Tests of homogeneity were performed and were not significant, i.e., it may be assumed that the different trials in each category estimate a common odds ratio even though definitions of progression and regression and of clinical events differ somewhat among the trials. The significance of the calculated pooled odds ratios as well as 95 percent confidence intervals (CI) were calculated. Paired comparisons between combined odds ratios for different trial groups were carried out using Bonferroni's correction for multiple comparisons. The clinical trials compared in these studies were the following:

Statin trials: LCAS, CIS, CARS, Post-CABG, REGRESS, PLAC I, CCAIT, MAAS, MARS

Surgical therapy: POSCH

Sequestrant Trials: STARS, NHLBI Type II

Lifestyle intervention: Heidelberg, STARS, Lifestyle Heart Trial

Combination drug therapy: HARP, SCRIP, SCOR, FATS (lovastatin/colestipol), FATS (nicotinic acid/colestipol), CLAS

Calcium channel blocker monotherapy trials: Montreal Heart Institute Study, INTACT

Both clinical trials and angiographic studies show reductions in CHD risk that are broadly consonant with what was projected from cohort studies. The issue of whether cholesterol-lowering therapy reduces total mortality is considered in detail subsequently (see Section II.9)

In recent trials, statin therapy reduced risk for CHD in men and women, in those with or without heart disease, in older and younger subjects, in those with diabetes and hypertension, and at most levels of cholesterol. These benefits for different subgroups are shown by meta-analysis prepared for ATP III by panel members and statistical consultants at NHLBI (Table II.2–3) and by a recent analysis from two combined secondary prevention trials (CARE and LIPID) (Sacks et al., 2000b; Rubins et al., 1999).

Table II.2–3. CHD Risk Reduction (RR) in Cholesterol Trial Subgroups

CHD Risk Reduction in Cholesterol Trial Subgroups							
Trait	**Subgroup**	**N**	**Mean RR**	**95% CI**		**P-Interaction***	**Trials†**
Gender	Male	21651	32%	26%	36%	0.759	AFCAPS, POSCH, CARE, LIPID, PLAC1, 4S, CCAIT
	Female	4147	34%	20%	45%		
Age	Younger	19119	33%	27%	39%	0.514	AFCAPS, POSCH, Upjohn, VAHIT, WOSCOPS, CARE, LIPID, PLAC1, CCAIT
	Older	16549	30%	24%	36%		
Hyper-tension	No	14623	33%	25%	39%	0.068	AFCAPS, POSCH, VAHIT, CARE, LIPID
	Yes	8520	22%	12%	31%		
Smoker	No	18343	23%	16%	30%	0.075	AFCAPS, POSCH, VAHIT, WOSCOPS, CARE, LIPID, Newcastle, CCAIT
	Yes	12193	32%	25%	39%		
Diabetes	No	25147	27%	21%	32%	0.596	AFCAPS, POSCH, VAHIT, CARE, LIPID, 4S
	Yes	2443	31%	17%	42%		
Choles-terol	Lower	14180	27%	20%	34%	0.480	POSCH, Upjohn, WOSCOPS, CARE, LIPID
	Higher	7519	32%	22%	40%		
LDL	Lower	11715	29%	22%	36%	0.012	AFCAPS, POSCH, VAHIT, WOSCOPS, CARE, LIPID, Helsinki
	Higher	16071	40%	35%	45%		
HDL	Lower	16739	33%	27%	38%	0.865	AFCAPS, POSCH, VAHIT, WOSCOPS, CARE, LIPID, Helsinki
	Higher	17021	34%	28%	39%		
TG	Lower	10791	30%	22%	38%	0.567	AFCAPS, POSCH, VAHIT, WOSCOPS, CARE, LIPID, Helsinki
	Higher	12192	27%	20%	34%		

* P-Interaction refers to the difference in treatment effect between the subgroups for each trait. The higher the number, the less is the difference in risk reduction between the two subgroups. The P-interaction term provides a statistical interpretation of the difference in relative risk reduction noted for the two subgroups. In statistical terms, the higher the number, the more homogeneous is the effect between the two subgroups. The dichotomous categories shown in this table vary in cutpoints depending on the results reported for each of the individual studies.

† See appendix for listing of the full names of these clinical trials.

Results of clinical trials of LDL lowering find support from a review of world-wide prospective studies on the relation between serum cholesterol levels and CHD incidence. In fact, Law et al. (Law et al., 1994b; Law 1999) reported a high congruence between results of prospective epidemiology studies and clinical trials. One advantage of epidemiological studies is their ability to examine and predict long-term influences. Earlier clinical trials found that a 1 percent reduction in serum total cholesterol level reduces risk for CHD by about 2 percent. Recent clinical trials with statins indicate that a 1 percent decrease in LDL cholesterol reduces risk by about 1 percent. However, across-country epidemiological studies strongly suggest that maintaining a lower serum cholesterol for periods longer than the duration of clinical trials yields a greater reduction in risk than is predicted from clinical trials. In populations that maintain very low cholesterol levels throughout life, the population risk for CHD is much lower than in populations that habitually carry higher cholesterol levels (Keys et al., 1980; 1984) In contrast, in high-risk populations, the reduction in CHD attained with aggressive cholesterol-lowering therapy still leaves absolute CHD rates far above those in low-risk populations. From another point of view, epidemiological studies suggest that beginning cholesterol-lowering therapy at an earlier age will lead to a greater risk reduction than starting later in life. For example, using data from a large number of cohort studies, Law et al. (Law et al., 1994b; Law 1999) found that a 10 percent reduction in serum cholesterol level attained at age 40 yields a reduction in relative risk for CHD of 50 percent at age 40, whereas a 10 percent cholesterol reduction gives only a 20 precent reduction in risk if begun at age 70. This finding implies that the greatest long-term benefit is attained by early intervention; conversely, later intervention yields lesser benefit in risk reduction.

Evidence statement: *Multiple lines of evidence from experimental animals, laboratory investigations, epidemiology, genetic forms of hypercholesterolemia, and controlled clinical trials indicate a strong causal relationship between elevated LDL cholesterol and CHD (A1, B1, C1).*
Recommendation: *LDL cholesterol should continue to be the primary target of cholesterol-lowering therapy.*

c. Categories and classification of total cholesterol and LDL cholesterol

ATP III maintains a classification of serum total cholesterol and LDL cholesterol similar to that in ATP II (National Cholesterol Education Program 1993; 1994) with some minor modifications. The ATP III classification is shown in Table II.2–4.

Table II.2–4. ATP III Classification of Total Cholesterol and LDL Cholesterol

Total Cholesterol (mg/dL)		LDL Cholesterol (mg/dL)	
		<100	Optimal
<200	Desirable	100–129	Near optimal/above optimal
200–239	Borderline High	130–159	Borderline High
≥240	High	160–189	High
		≥190	Very High

3. Other lipid risk factors

a. Triglycerides

1) Elevated serum triglycerides (and triglyceride-rich lipoproteins) as a risk factor

Many prospective epidemiological studies have reported a positive relationship between serum triglyceride levels and incidence of CHD (Austin et al., 1998; Assmann et al., 1998a). However, early multivariate analyses generally did not identify serum triglycerides as an independent risk factor for CHD (Hulley et al., 1980). This failure results from the large number of intercorrelated variables associated with elevated triglycerides. Lipoprotein metabolism is integrally linked, and elevations of serum triglycerides can be confounded by significant correlations with total, LDL, and HDL-cholesterol levels. Nonlipid risk factors of obesity, hypertension, diabetes, and cigarette smoking are also interrelated with triglycerides (Grundy 1998a) as are several emerging risk factors (insulin resistance, glucose intolerance, and prothrombotic state [see Section II.5]). Thus, many persons with elevated triglycerides are at increased risk for CHD, even when this greater risk cannot be independently explained by triglycerides. Still, renewed interest in the importance of elevated triglycerides has been stimulated by the publication of meta-analyses that found that raised triglycerides are in fact an *independent risk factor* for CHD (Austin et al., 1998; Assmann et al., 1998a). This independence suggests that some triglyceride-rich lipoproteins (TGRLP) are atherogenic.

2) Lipoprotein remnants as atherogenic lipoproteins

The most likely candidates for atherogenic TGRLP are remnant lipoproteins. These lipoproteins include small, VLDL and IDL. They are cholesterol-enriched particles and have many of the properties of LDL. Reviews of several independent lines of evidence support the atherogenicity of remnants (Havel 1990; Krauss 1998; Grundy 1998a). Specific evidence can be cited. In experimental animals, cholesterol-enriched remnants definitely cause atherosclerosis (Nordestgaard and Lewis, 1991; Breslow 1996). Genetic hyperlipidemias characterized by the accumulation of lipoprotein remnants commonly produce premature CHD and peripheral vascular disease in humans (Weisgraber et al., 1990; Mahley et al., 1991). In several clinical studies in which remnants were specifically identified, their elevations emerged as strong predictors of coronary atherosclerosis or CHD (Tatami et al., 1981; Steiner et al., 1987; Krauss

et al., 1987; Phillips et al., 1993; Tornvall et al., 1993; Hodis et al., 1994; Koren et al., 1996; Karpe et al., 2001; Takeichi et al., 1999; Thompson 1998; Sacks et al., 2000a). This relation of remnants to CHD was also noted in several reviews (Krauss 1998; Grundy 1998a). Finally, drug therapies that reduce remnant lipoproteins (fibrates, nicotinic acid, and statins) are accompanied by reduced risk for CHD (see Section II.3.d.).

3) VLDL cholesterol as a marker for remnant lipoproteins

Although a variety of methods have been developed to identify lipoprotein remnants, most are not applicable to clinical practice; the most readily available measure for clinical practice is VLDL cholesterol. Some cholesterol in VLDL may reside in non-atherogenic TGRLP, but most of it apparently occurs in atherogenic remnants (Kuchinskiene and Carlson, 1982; Miller and Small, 1983; Tatami et al., 1981; Bjorkegren et al., 2000). Thus, VLDL cholesterol, as a marker for remnant lipoproteins, is a potential target of cholesterol-lowering therapy.

4) Causes of elevated serum triglyceride

Several causes underlie elevated triglycerides in the general population (Stone 1994; Chait and Brunzell, 1990).

- Overweight and obesity
- Physical inactivity
- Cigarette smoking
- Excess alcohol intake
- Very high-carbohydrate diets (>60 percent of total energy)
- Other diseases (type 2 diabetes, chronic renal failure, nephrotic syndrome)
- Certain drugs (corticosteroids, protease inhibitors for HIV, beta-adrenergic blocking agents, estrogens)
- Genetic factors

In persons with none of these factors, serum triglyceride levels typically are less than 100 mg/dL (Heiss et al., 1980). As some of these triglyceride-raising factors develop, levels commonly rise into the range of 150 to 199 mg/dL (Denke et al., 1993; 1994). Although several factors can elevate triglycerides (see above), most common are overweight/obesity and physical inactivity (Denke et al., 1993; 1994; National Institutes of Health 1998a,b; Hardman 1999; Berg et al., 1997). When triglycerides rise to $\geq$200 mg/dL, these latter factors may contribute, but genetic influences play an increasing role as well (Goldstein et al., 1973b).

5) Categories of serum triglycerides

ATP II (National Cholesterol Education Program 1993; 1994) adopted conservative definitions of serum triglyceride ranges based on the perceived weak independent relationship of triglycerides to CHD. Multivariate analysis of prospective studies at that time suggested that higher triglycerides carry little independent risk for CHD. After review of more recent evidence, the ATP III panel concluded that the link between serum triglycerides and CHD is stronger than previously recognized. Elevated triglycerides are widely recognized as a marker for increased

risk, as revealed in univariate analysis (Hulley et al., 1980; Austin et al., 1998; Assmann et al., 1998a). In this context elevations in serum triglycerides can be considered a marker for atherogenic remnant lipoproteins, for other lipid risk factors (small LDL particles and low HDL), for other nonlipid risk factors (elevated blood pressure), and for emerging risk factors (insulin resistance, glucose intolerance, prothrombotic state) (Grundy 1998a). Thus, the finding of elevated serum triglycerides helps to identify persons who are at risk and who need intervention for risk reduction. In addition, when triglyceride levels are ≥200 mg/dL, the presence of increased quantitites of atherogenic remnant lipoproteins can heighten CHD risk substantially beyond that predicted by LDL cholesterol alone (Steiner et al., 1987; Havel 2000). For these reasons, ATP III modified the triglyceride classification to give more attention to moderate elevations.

Table II.3–1 compares the older ATP II classification with the new ATP III classification for serum triglycerides.

Table II.3–1. Classification of Serum Triglycerides

Triglyceride Category	ATP II Levels	ATP III Levels
Normal triglycerides	<200 mg/dL	<150 mg/dL
Borderline-high triglycerides	200–399 mg/dL	150–199 mg/dL
High triglycerides	400–1000 mg/dL	200–499 mg/dL
Very high triglycerides	>1000 mg/dL	≥500 mg/dL

6) Elevated serum triglycerides and triglyceride-rich lipoproteins as targets of therapy

Elevated triglycerides represent one factor within a set of risk-factor targets in persons who are overweight, obese, sedentary, or cigarette smokers. Life-habit changes—weight control, exercise, and smoking cessation—will favorably modify multiple risk factors including elevated triglycerides (National Institutes of Health 1998a,b). Thus, elevated serum triglycerides are a potential target for therapeutic lifestyle changes.

Among triglyceride targets, remnant lipoproteins are the strongest candidates for direct clinical intervention designed to reduce risk for CHD. Atherogenic remnants can be lowered by weight reduction in overweight and obese persons (Wilson et al., 1992) and by lipid-lowering drugs (statins, fibrates, and nicotinic acid) (Vega and Grundy, 1985; 1990b; 1994; Mostaza et al., 1997). However, none of these therapies reduce only remnants; they modify either concentrations or characteristics of all lipoprotein species. This makes it difficult to confirm the efficacy of lowering remnants per se through clinical trials. Nonetheless, the strong evidence for independent atherogenicity of elevated remnants makes them appropriate targets for cholesterol-lowering therapy (Reardon et al., 1985; Steiner et al., 1987; Havel 2000).

Evidence statements: *Elevated serum triglycerides are associated with increased risk for CHD (C1). In addition, elevated triglycerides are commonly associated with other lipid and nonlipid risk factors (C1).*
Recommendation: *Greater emphasis should be placed on elevated triglycerides as a marker for increased risk for CHD. First-line therapy for elevated serum triglycerides should be therapeutic lifestyle changes.*

Evidence statement: *Some species of triglyceride-rich lipoproteins, notably, cholesterol-enriched remnant lipoproteins, promote atherosclerosis and predispose to CHD (C1).*
Recommendation: *In persons with high serum triglycerides, elevated remnant lipoproteins should be reduced in addition to lowering of LDL cholesterol.*

b. Non-HDL cholesterol

1) Non-HDL cholesterol as a risk factor

Since VLDL cholesterol is highly correlated with atherogenic remnant lipoproteins, it can reasonably be combined with LDL cholesterol to enhance risk prediction when serum triglycerides are high. The sum of VLDL+LDL cholesterol is called non-HDL cholesterol. It is calculated routinely as total cholesterol minus HDL cholesterol. Non-HDL cholesterol includes all lipoproteins that contain apo B. In persons with high triglycerides (200–499 mg/dL) most cholesterol occurring in the VLDL fraction is contained in smaller (remnant) VLDL (Kuchinskiene and Carlson, 1982; Steiner et al., 1987; Miller and Small, 1983; Tatami et al., 1981; Bjorkegren et al., 2000). Few prospective studies have explicitly examined the predictive power of non-HDL-cholesterol levels versus LDL-cholesterol levels in a large group of persons with hypertriglyceridemia. However, Gordon et al. (Gordon et al., 1989) reported that because non-HDL cholesterol and HDL cholesterol are intercorrelated, they overlap in prediction, whereas LDL cholesterol is independent of HDL cholesterol as a predictor. Thus, some of the predictive power usually attributed to HDL cholesterol could be explained by elevations of non-HDL cholesterol. Frost and Havel (1998) proposed that existing data actually favor use of non-HDL cholesterol over LDL cholesterol in clinical evaluation of risk. This proposal is strengthened by a recent report from the follow-up of the Lipid Research Clinic cohort which showed a stronger correlation with coronary mortality for non-HDL cholesterol than for LDL cholesterol (Cui et al., 2001). Moreover, non-HDL cholesterol is highly correlated with total apolipoprotein B (apo B) (Vega and Grundy, 1990a; Abate et al., 1993); apolipoprotein B is the major apolipoprotein of all atherogenic lipoproteins. Serum total apo B also has been shown to have a strong predictive power for severity of coronary atherosclerosis and CHD events (Sedlis et al., 1986; Sniderman 1988; Marcovina et al., 1988; Reinhart et al., 1990; Sniderman et al., 1991; Levinson and Wagner, 1992; Kwiterovich et al., 1992; Tornvall et al., 1993; Westerveld et al., 1998; Gotto et al., 2000; Lamarche et al., 1996; Lemieux et al., 2000). Because of the high correlation between non-HDL cholesterol and apolipoprotein B levels (Vega and Grundy, 1990a; Abate et al., 1993), non-HDL cholesterol represents an acceptable surrogate marker for total apolipoprotein B in routine clinical practice; standardized measures of apolipoprotein B are not

widely available for routine measurement. Potential uses of non-HDL cholesterol are for initial testing or for monitoring of response in the nonfasting state; the measurement is reliable in nonfasting serum, whereas calculated LDL cholesterol can be erroneous in the presence of postprandial hypertriglyceridemia.

In most persons with triglyceride levels <200 mg/dL, VLDL cholesterol is not substantially elevated (Lipid Research Clinics Program Epidemiology Committee 1979), and further, non-HDL cholesterol correlates highly with LDL cholesterol (Vega and Grundy, 1990a; Abate et al., 1993); therefore, adding VLDL cholesterol to LDL cholesterol at lower triglyceride levels would be expected to provide little additional power to predict CHD. When triglyceride levels are ≥200 mg/dL, VLDL cholesterol levels are distinctly raised (Lipid Research Clinics Program Epidemiology Committee 1979), and LDL-cholesterol concentrations are less well correlated with VLDL and LDL (non-HDL) cholesterol levels (Vega and Grundy, 1990a; Abate et al., 1993); consequently, LDL cholesterol alone inadequately defines the risk associated with atherogenic lipoproteins. In the presence of high serum triglycerides, non-HDL cholesterol therefore will better represent the concentrations of all atherogenic lipoproteins than will LDL cholesterol alone. On the other hand, when triglyceride levels become very high (e.g., ≥500 mg/dL) some of the cholesterol in TGRLP resides in nonatherogenic forms of larger VLDL and chylomicrons, and non-HDL cholesterol may be less reliable as a predictor of CHD risk.

2) Non-HDL cholesterol as a secondary target of therapy

Clinical trials of cholesterol-lowering therapy have not specifically identified non-HDL cholesterol (independent of LDL) as a target of therapy; thus, it has been difficult to isolate the impact of lowering non-HDL cholesterol per se on CHD risk. However, the same statement could be made about LDL itself. For example, it has been widely assumed from primary and secondary prevention trials of statin therapy that risk reduction is a response to LDL cholesterol lowering. Of interest, however, the percentage reductions of LDL cholesterol and VLDL cholesterol on statin therapy are similar (Vega and Grundy, 1990a).

Consequently, it is not possible to differentiate risk reduction due to LDL lowering from non-HDL cholesterol lowering. Most clinical trials have not specifically included persons with hypertriglyceridemia; thus it can be assumed that lowering of VLDL cholesterol was a minor contributor to risk reduction in statin trials. However, in clinical practice, the situation may be different; when triglycerides are high, a significant fraction of non-HDL cholesterol is contained in VLDL. Here LDL cholesterol may not be the only significant lipid risk factor. Consequently, when triglycerides are high, non-HDL cholesterol (including VLDL cholesterol) can serve as a secondary target of therapy.

A "normal" VLDL cholesterol can be defined as that present when triglycerides are <150 mg/dL; this value typically is ≤30 mg/dL (Lipid Research Clinics Program Epidemiology Committee 1979). Conversely, when triglyceride levels are >150 mg/dL, VLDL cholesterol usually is >30 mg/dL. Thus, a reasonable goal for non-HDL cholesterol is one that is 30 mg/dL higher than the LDL-cholesterol goal. A specific goal of therapy for serum triglycerides is not identified in ATP III for two reasons: (a) triglyceride levels have more day-to-day variability than non-HDL-cholesterol levels and thus are less reliable, and (b) non-HDL cholesterol as a target allows more flexibility in choice of therapies to reduce atherogenic lipoproteins contained in the combined

LDL+VLDL fraction. Non-HDL cholesterol was chosen as a preferred secondary target of therapy over total apo B for three other reasons: (a) standardized measures of total apo B are not widely available in clinical practice; (b) measures of total apo B have not been shown in a large number of prospective studies to carry greater predictive power than non-HDL cholesterol in persons with elevated triglycerides; and (c) measurement of total apo B will constitute an added expense beyond the usual lipoprotein profile.

Evidence statements: *Some species of triglyceride-rich lipoproteins are independently atherogenic; notable among these are cholesterol-enriched remnant lipoproteins (C1). Moreover, VLDL cholesterol is a marker for atherogenic VLDL remnants (C1).*
Recommendation: *In persons with high triglycerides (≥200 mg/dL), VLDL cholesterol should be combined with LDL cholesterol, yielding non-HDL cholesterol. The latter constitutes "atherogenic cholesterol" and should be a secondary target of therapy.*

c. High density lipoproteins (HDL)

1) Low HDL cholesterol as an independent risk factor for CHD

Strong epidemiological evidence links low levels of serum HDL cholesterol to increased CHD morbidity and mortality (Wilson et al., 1998; Gordon et al., 1989; Abbott et al., 1988). High HDL-cholesterol levels conversely convey reduced risk. Epidemiological data taken as a whole signify that a 1 percent decrease in HDL cholesterol is associated with a 2–3 percent increase in CHD risk (Gordon et al., 1989). Epidemiological studies consistently show low HDL cholesterol to be an *independent risk factor* for CHD. Its independent relationship holds after correction for other risk variables in multivariate analysis. In fact, in prospective studies (Wilson et al., 1980; Assmann et al., 1996), HDL usually proves to be the lipid risk factor most highly correlated with CHD risk. ATP II specified low HDL cholesterol (<35 mg/dL) as one of several major risk factors used to modify the therapeutic goal for LDL cholesterol. The definition of a low HDL was set to be the same for both men and women because of the view that a given level of HDL would impart the same risk for men and women.

The mechanistic relationship between low HDL-cholesterol levels and occurrence of CHD has not been fully elucidated. One theory holds that HDL directly participates in the atherogenic process. Some research in laboratory animals backs a direct action. In genetically modified animals, high levels of HDL appear to protect against atherogenesis (Rubin et al., 1991; Plump et al., 1994; Tangirala et al., 1999). In vitro, HDL promotes efflux of cholesterol from foam cells in atherosclerotic lesions (reverse cholesterol transport) (Tall 1998). Recent studies indicate that the antioxidant and anti-inflammatory properties of HDL also inhibit atherogenesis (van Lenten et al., 1995; Navab et al., 2000a,b). Further, some genetic forms of HDL deficiency are accompanied by increased risk for CHD (Ng et al., 1995; Miller et al., 1998); others appear not to be (Romling et al., 1994; Takata et al., 1995; Miccoli et al., 1996). This latter finding raises the possibility that some subspecies of HDL affect atherogenesis whereas others do not. Although there are conflicting data, multiple lines of evidence strongly intimate that HDL plays a direct role in the atherogenic process. If so, it is a potential target for therapy.

The direct role of HDL in atherogenesis probably cannot fully account for the strong predictive power of HDL in epidemiological studies. A low HDL level correlates with the presence of other atherogenic factors (Vega and Grundy, 1996). In many persons, a low HDL level correlates with elevations of serum triglycerides and remnant lipoproteins (Schaefer et al., 1994; Phillips et al., 1981); in addition, low HDL commonly shows linkage with small, dense LDL particles (Austin et al., 1990; Luc et al., 1997; Rainwater 2000; Austin et al., 2000b). The tight association among low HDL, small LDL particles, and elevated triglycerides has evoked the term *lipid triad.* Moreover, a low HDL level can be a sign of insulin resistance and its associated metabolic risk factors (Vega and Grundy, 1996) (see Section II.6 Metabolic Syndrome). Because of the association of low HDL with other atherogenic factors (some of which are not included among standard risk factors), a low HDL cholesterol is not as strongly *independent* in its prediction of CHD as suggested by usual multivariate analysis, i.e., its independence is partially confounded by some risk factors that are not routinely measured, e.g., *emerging risk factors* (see Section II.5). This confounding raises the possibility that therapeutic raising of HDL-cholesterol levels will not reduce CHD risk as much as might be predicted from prospective epidemiological studies (Vega and Grundy, 1996).

Evidence statement: *A low HDL-cholesterol level is strongly and inversely associated with risk for CHD (C1).*

2) Causes of low HDL cholesterol

There are several factors that contribute to low HDL-cholesterol levels that need to be identified in clinical practice (Krauss 1982; Stone 1994; Chait and Brunzell, 1990). These include:

- Elevated serum triglycerides
- Overweight and obesity
- Physical inactivity
- Cigarette smoking
- Very high carbohydrate intakes (>60 percent of total energy intake)
- Type 2 diabetes
- Certain drugs (beta-blockers, anabolic steroids, progestational agents)
- Genetic factors

In the general population, about 50 percent of the variability of serum HDL-cholesterol levels derives from genetic factors (Cohen et al., 1994); the other 50 percent presumably comes from the acquired factors listed above. Moreover, when a person has a genetic predisposition to reduced HDL, acquired factors often drive HDL cholesterol to categorically low levels. Among these acquired factors, overweight and obesity appear to be most important (National Institutes of Health 1998a,b; Brown CD et al., 2000). Part of the effect of overweight and obesity can be explained by their action to raise serum triglycerides, which lowers HDL-cholesterol levels, but they probably reduce HDL cholesterol through other mechanisms as well (Nie et al., 1998; Carr et al., 1999; Tato et al., 1995).

3) Classification of serum HDL cholesterol

The inverse association between HDL-cholesterol concentrations and CHD risk is a continuous variable; no threshold relationship has been identified (Wilson et al., 1998). For this reason, any categorical definition of low HDL cholesterol must be arbitrary. In ATP II (National Cholesterol Education Program 1993; 1994), a low HDL cholesterol was defined as a level <35 mg/dL; the setting of this cutpoint was influenced by the concept that low HDL is primarily a direct cause of atherosclerotic disease. More recently, the role of HDL as an indicator of other risk correlates has been emphasized (Vega and Grundy, 1996; Karhapaa et al., 1994; Lamarche et al., 1993; Assmann et al., 1992). This shift in perception requires a re-examination of the appropriate cutpoint for low HDL. Clearly low HDL levels predict CHD at levels above 35 mg/dL (Wilson et al., 1998); this fact combined with the moderate reductions of HDL cholesterol caused by obesity and physical inactivity led the ATP III panel to recognize a somewhat higher HDL-cholesterol level as a categorical risk factor. The level <40 mg/dL was set as a low HDL cholesterol, both in men and women. Women typically have higher HDL cholesterol levels than men, and a cutpoint of <40 mg/dL will identify more men than women with low HDL cholesterol, i.e., approximately one-third of men and about one-fifth of women in the general population. Setting a different cutpoint for categorical low HDL cholesterol for men and women was rejected because it would make many women who are otherwise at low risk eligible for LDL-lowering drugs. On the other hand, as will be discussed subsequently, a higher level of HDL cholesterol (<50 mg/dL) is defined as a marginal risk factor in women, which will mandate more intensive lifestyle therapies (weight reduction and increased physical activity) (see Section II.6, Metabolic Syndrome).

In prospective studies, including the Framingham Heart Study (Wilson et al., 1998), a high HDL cholesterol is associated with reduced risk for CHD. In ATP II, this level (*high HDL cholesterol)* was also called a *negative risk factor,* and its presence evoked removal of one risk factor from the risk factor count used for setting treatment goals for LDL cholesterol. ATP III affirms the validity of this assignment. The ATP III classification of HDL cholesterol thus is given in Table II.3–2.

Table II.3–2. ATP III Classification of HDL Cholesterol

Serum HDL Cholesterol (mg/dL)	
<40 mg/dL	Low HDL cholesterol
≥60 mg/dL	High HDL cholesterol

Evidence statement: *Population studies show a continuous rise in risk for CHD as HDL-cholesterol levels decline (C1). Higher risk for CHD at lower HDL levels is multifactorial in causation (C1). Although the inverse relationship between HDL cholesterol and CHD shows no inflection points, any reduction in HDL cholesterol from population means is accompanied by increased risk for CHD (C1).*
Recommendation: *A categorical low HDL cholesterol should be defined as a level of <40 mg/dL, in both men and women.*

4) Low HDL cholesterol as a potential target of therapy

Persons with low HDL-cholesterol levels benefit similarly to those with higher HDL cholesterol during LDL-lowering therapy (Table II.2–3). Whether raising HDL per se will reduce risk for CHD has not been resolved. Nonetheless, HDL levels are raised to varying degrees with lipid-modifying drugs, e.g., nicotinic acid (Martin-Jadraque et al., 1996), fibrates (Frick et al., 1987; Rubins et al., 1999), and statins (Kastelein et al., 2000). Furthermore, clinical trials with nicotinic acid (Coronary Drug Project . . . 1975) and fibrates (Frick et al., 1987; Rubins et al., 1999) provide suggestive evidence that HDL raising provides one component of risk reduction with these drugs. Whether the small rise in HDL-cholesterol levels accompanying statin therapy accounts for any of the risk reduction from these drugs is uncertain. Since currently available drugs have multiple actions, it is difficult to dissect fully the benefit of HDL raising from that of reducing atherogenic lipoproteins. Regardless, use of drugs that favorably modify multiple inter-related lipid risk factors appears to reduce risk for CHD (see Section II.3.d, Atherogenic Dyslipidemia). Finally, raising HDL levels by reversal of the major acquired causes of low HDL levels—overweight and obesity, physical inactivity, and smoking—provides the opportunity for further risk reduction in persons with low HDL-cholesterol levels. In addition, modifying these causes will be beneficial for other reasons besides raising HDL-cholesterol concentrations.

Evidence statements: *Clinical trials provide suggestive evidence that raising HDL-cholesterol levels will reduce risk for CHD (A2). However, it remains uncertain whether raising HDL-cholesterol levels per se, independent of other changes in lipid and/or nonlipid risk factors, will reduce risk for CHD.*
Recommendation: *A specific HDL-cholesterol goal level to reach with HDL-raising therapy is not identified. However, nondrug and drug therapies that raise HDL-cholesterol levels and are part of management of other lipid and nonlipid risk factors should be encouraged.*

d. Atherogenic dyslipidemia

A common form of dyslipidemia is characterized by three lipid abnormalities: elevated triglycerides, small LDL particles, and reduced HDL cholesterol (Austin et al., 1998; Krauss 1998; Grundy 1998a). Often the lipoprotein concentrations in this *lipid triad* are not categorically abnormal, but are only marginally deranged. More sophisticated methodology than that used in routine clinical practice can identify these multiple interrelated abnormalities. Still, in some persons, low HDL-cholesterol levels can occur in the absence of other lipoprotein abnormalities. These persons are said to have *isolated low HDL.* They are not common in the general population, however; more often, low HDL cholesterol occurs as a component of the lipid triad. Because of the common occurrence of the lipid triad, the relation of the lipid triad as a whole to CHD risk will be considered, and whether the entire triad is a target for therapy.

1) Atherogenic dyslipidemia as a "risk factor"

The lipid triad occurs commonly in persons with premature CHD (Austin et al., 1990; Austin et al., 1988), hence the designation *atherogenic lipoprotein phenotype* or *atherogenic*

dyslipidemia. Typical characteristics of persons with atherogenic dyslipidemia are obesity, abdominal obesity, insulin resistance, and physical inactivity (National Institutes of Health 1998a,b). Many persons with type 2 diabetes have atherogenic dyslipidemia (Verges 1999; Durrington 1999; Kreisberg 1998*).* In epidemiological studies in high-risk populations, the contributions of individual components of atherogenic dyslipidemia to CHD risk cannot reliably be dissected from the sum of lipid risk factors. Although there is evidence that each component of the lipid triad—low HDL, small LDL, and remnant lipoproteins—is individually atherogenic, the relative quantitative contribution of each cannot be determined. For this reason, it is reasonable to view the lipid triad as a whole as a "risk factor."

2) Atherogenic dyslipidemia as a target of therapy

Most therapies that lower triglyceride or raise HDL cholesterol actually modify all of the components of the lipid triad. Weight reduction in overweight and obese subjects favorably modifies atherogenic dyslipidemia (National Institutes of Health 1998a,b); so does increased physical activity (Kokkinos and Fernhall, 1999). Among lipid-lowering drugs, fibrates and nicotinic acid specifically improve all of the elements of the lipid triad (Guyton et al., 2000; Zema 2000; Martin-Jadraque et al., 1996; Vega and Grundy, 1994). Therefore, in considering clinical trial evidence of benefit from therapeutic modification of atherogenic dyslipidemia, all therapeutic responses together rather than individual responses in individual lipoprotein species likely determine efficacy. Although attempts have been made to dissect apart the contributions of changes in individual lipoprotein species, the conclusions are always dubious. Tables II.3–3 and II.3–4 summarize the results of clinical trials in which drugs that modify atherogenic dyslipidemia—fibrates and nicotinic acid—were used. Table II.3–3 shows results of primary prevention trials, whereas Table II.3–4 summarizes secondary prevention trials. The trials taken as a whole show a strong trend towards reduction in CHD risk through therapeutic modification of atherogenic dyslipidemia.

Table II.3–3. Primary Prevention Clinical Trials with CHD Endpoints Using Drugs that Modify Triglyceride-Rich Lipoproteins

Primary prevention

Trial/Drug/ Duration of Intervention	Number of Subjects	Baseline or Placebo Lipid and Lipoprotein Values and On-Treatment Lipid and Lipoprotein in Drug Treatment Group					Percent change coronary event rate (Drug vs. Placebo Groups)
		Group	TC (mg/dL)	TG (mg/dL)	Non-HDL-C (mg/dL)	HDL-C (mg/dL)	
WHO trial* Clofibrate 5 yrs	15,745 men lipids from Edinburgh (Subsets: n = 4935)	Placebo	257	210	—	—	-20% (p=0.05)
		On-Treatment	229	160	—	—	
Helsinki Heart Study† Gemfibrozil 5 yrs	4,081 men	Baseline	289	175	242	47	-34% (p<0.02)
		On-Treatment	247	115	196	51	

Abbreviations: TC = total cholesterol; TG = triglycerides; non-HDL-C = non-HDL cholesterol; HDL-C = HDL cholesterol.

* Committee of Principal Investigators 1978.

† Frick et al., 1987.

Table II.3–4. Secondary Prevention Clinical Trials with CHD Endpoints Using Drugs that Modify Triglyceride-Rich Lipoproteins

Trial/Drug/ Duration of Intervention	Number of Subjects	Baseline or Placebo Lipid and Lipoprotein Values and On-Treatment Lipid and Lipoprotein in the Drug-Treatment Group					% Change in Coronary Event Rate (Drug vs. Placebo Groups)
		Group	TC (mg/dL)	TG (mg/dL)	Non-HDL-C (mg/dL)	HDL-C (mg/dL)	
Coronary Drug Project* Clofibrate 5 yrs	1,103 men on Clofibrate Treatment vs. 2,789 placebo	Baseline	250	177	—	—	-5% (ns)
		On-Treatment	234	149	—	—	
Coronary Drug Project* Nicotinic acid 5 yrs	1,119 Rx men; 2,789 placebo	Baseline	250	177	—	—	-22% p<0.05
		On-Treatment	226	143	—	—	
Newcastle Trial† Clofibrate 5 yrs	400 men	Baseline	245	337	—	—	-49% p<0.01
		On-Treatment	217	215	—	—	
	97 women	Baseline	270	—	—	—	
		On-Treatment	229	—	—	—	
Scottish Trial‡ Clofibrate 6 yrs	593 men	Baseline	264	—	—	—	-44% (ns)
		On-Treatment	229	—	—	—	
	124 women	Baseline	280	—	—	—	
		On-Treatment	228	—	—	—	
Stockholm Study¥ Clofibrate+ Nicotinic acid 5 yrs	219 men 60 women lipoproteins on subset	Baseline	251	208	203	48	-36% p<0.01
		On-Treatment	218	166	—	—	
VA-HIT trial§ Gemfibrozil 5 yrs	2,531 men	Baseline	175	161	143	32	-22% p<0.006
		On-Treatment	170	115	136	34	
BIP£ Bezafibrate 6 yrs	2,825 men 265 women	Baseline	212	145	177	35	-9.4% p = 0.26
		On-Treatment	202	115	161	41	

* Coronary Drug Project Research Group 1975.

† Group of Physicians of the Newcastle-upon-Tyne Region 1971.

‡ Research Committee of the Scottish Society of Physicians.

¥ Carlson and Rosenhamer 1988.

§ Rubins et al., 1999.

£ Bizafibrate Infarction Prevention Study 2000.

In addition to the end-point trials shown in Tables II.3–3 and II.3–4, three trials of fibrate therapy have been carried out in which the end-points are coronary atherosclerosis as assessed by angiography. The results of these trials are summarized in Table II.3–5. They show that fibrate therapy on average causes a reduction in minimum lesion diameter of coronary arteries, without appreciably reducing LDL cholesterol.

Table II.3–5. Clinical Trials with Angiographic Endpoints Using Drugs that Modify Triglyceride-Rich Lipoproteins in Persons with Established Coronary Disease or CHD Equivalent

Trial/Drug/ Duration of intervention	N	Baseline and Rx Lipid and Lipoprotein Values					Mean change, minimum lesion diameter (mm)*
		Group	Total Chol	TG	LDL	HDL	
BECAIT† Bezafibrate 600 mg 5 yr	92 men; 80% had mixed dyslipidemia	Baseline	266	216	180	34	-0.17 placebo -0.06 bezafibrate p<0.05
		On-Treatment	229	159	173	37	
LOCAT‡ Gemfibrozil 1200mg 2–3 yr	395 men with Low HDL, all s/p CABG	Baseline	199	146	139	31	-0.04 placebo -0.01 gemfibrozil p=0.009
		On-Treatment	186	92	130	38	
DAIS¥ Fenofibrate	305 men 113 women with Type 2 Diabetes	Baseline	216	214	133	40	-0.06 placebo -0.01 fenofibrate p<0.029
		On-Treatment	~194	~154	~125	~43	

* Lower numbers signify less progression of lesions.

† Ericsson et al., 1996.

‡ Frick et al., 1997.

¥ DAIS Investigators 2001.

Finally, two trials of combined drug therapy have assessed changes in coronary lumen diameter; in these trials, one drug was an LDL-lowering drug and another targeted atherogenic dyslipidemia (Table II.3–6). In both, drug therapy produced favorable changes in coronary lesions.

Table II.3–6. Treatment of Atherogenic Dyslipidemia with Drugs in Combination with LDL-Lowering Sequestrants or Statins

Trial/Drug/ Duration of intervention	N	Baseline and Rx Lipid and Lipoprotein Values in Drug Group					Mean change, minimum lesion diameter (mm)*
		Group	Total Chol	TG	LDL	HDL	
CLAS[†] Niacin 3–12g + colestipol 30g 2 yrs	162 male nonsmokers s/p CABG	Baseline	246	151	171	45	-0.06 placebo +0.02N+C p<0.01
		On-Treatment	180	110	97	61	
FATS[‡] Niacin 4–6g + colestipol 30g 2 yrs	146 men with CAD and high Apo B levels	Baseline	270	194	190	39	-0.05 usual care +0.04N+C p=0.005
		On-Treatment	209	137	129	55	
HATS[¥] Niacin 2–4 g + Simvastatin 10–20 mg	160 (24 women, 136 men) with CAD, low HDL, normal LDL	Baseline	201	213	125	31	-0.14 -0.01 p<0.001
		On-Treatment	139	126	75	40	

* Positive numbers indicate net regression, compared to negative numbers which denote progression of lesions. N = niacin; C = colestipol.

† Blankenhorn et al., 1987.

‡ Brown et al., 1990.

¥ Brown BG et al., 2000.

Taken together, these various clinical trials support a beneficial effect of drugs that favorably modify atherogenic dyslipidemia on coronary lesions and major coronary events.

Evidence statements: *Atherogenic dyslipidemia commonly occurs in persons with premature CHD (C1). Moreover, atherogenic dyslipidemia strongly associates with abdominal obesity, obesity, and physical inactivity (C1). Weight reduction and increased physical activity will mitigate atherogenic dyslipidemia (A1).*

Recommendation: *For management of atherogenic dyslipidemia, emphasis in management should be given to life-habit modification—weight control and increased physical activity.*

Evidence statement: *Drugs that modify atherogenic dyslipidemia yield a moderate reduction in CHD risk (A2, B2).*

Recommendation: *Consideration should be given to treatment of atherogenic dyslipidemia with specific drug therapy, i.e., fibrates or nicotinic acid, in higher risk persons.*

4. Nonlipid risk factors

A number of nonlipid risk factors are associated with increased CHD risk and must be considered in preventive efforts. Some of these factors are modifiable and are appropriate targets for intervention efforts in themselves (Table II.4–1). Several fixed risk factors cannot be modified; their presence signals the need for more intensive lowering of LDL cholesterol. ATP I/II and other guidelines have advocated adjusting the intensity of LDL-cholesterol therapy in the primary prevention setting according to the absolute risk for CHD. In addition, emerging risk factors promise to provide new insights into the atherosclerotic process and potentially refine risk assessment. Certainly not all of coronary risk can be explained by the major independent risk factors. Other risk factors, some of which are yet to be identified, undoubtedly influence risk independently of the major risk factors. Some of these other factors contributing to CHD risk include the life-habit risk factors (obesity, physical inactivity, and atherogenic diet), emerging risk factors, male sex, and genetic/racial/ethnic characteristics. This section will review the established nonlipid risk factors including the life-habit risk factors. The emerging risk factors are reviewed in Section II.5. The influence of racial/ethnic characteristics on risk are discussed in more detail in Section IX.

Table II.4–1. Nonlipid Risk Factors for CHD

Modifiable Risk Factors	Nonmodifiable Risk Factors
Hypertension*	Age*
Cigarette Smoking*	Male Sex*
Thrombogenic/hemostatic state†	Family History of Premature CHD*
Diabetes‡	
Obesity	
Physical inactivity	
Atherogenic diet	

* Risk factors that are included in the ATP III CHD risk assessment algorithm.

† This risk factor is inferred from observations that antiplatelet drugs and anticoagulants have been shown to reduce risk for CHD.

‡ Modification of blood pressure and lipids in people with diabetes has been shown to reduce CHD risk. Clinical trials of improved glucose control show a trend to CHD risk reduction, but not a statistically significant reduction.

A first aim for people with modifiable nonlipid risk factors is to alter them to reduce CHD risk. Risk reduction therapies consist of smoking cessation, control of hypertension, weight reduction, increased physical activity, and improved nutrition. Control of diabetic hyperglycemia will prevent microvascular complications, although clinical trials have not unequivocally demonstrated that improved glucose control lowers CHD events. Modification of blood pressure and lipids in people with diabetes, however, does reduce CHD risk (see discussion below). In addition, the recommendations for cholesterol management operationally take selected factors into account by setting lower thresholds for initiating treatment and lower goal levels for LDL cholesterol for those at higher risk (Table II.4–2). A low HDL cholesterol (<40 mg/dL) also counts as a major risk factor for setting lower LDL goals, whereas a higher HDL cholesterol

(≥60 mg/dL) takes away one other risk factor. Evidence relating the nonlipid risk factors to CHD is summarized below (Sections II.4.a and II.4.b).

Table II.4–2.

Primary Prevention: Risk Status Based on Presence of CHD Risk Factors Other Than LDL Cholesterol

Positive Risk Factors

1. Age

   Male: ≥45 years

   Female: ≥55 years

2. Family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative, or before 65 years of age in mother or other female first-degree relative)
3. Current cigarette smoking
4. Hypertension (≥140/90 mmHg,* or on antihypertensive medication)
5. Low HDL cholesterol (<40 mg/dL*)

Negative (protective) Risk Factor†

6. High HDL cholesterol (≥60 mg/dL)

High risk, defined as a net of two or more CHD risk factors, leads to more vigorous intervention in primary prevention. Age (defined differently for men and for women) is treated as a risk factor because rates of CHD are higher in the older than in the young, and in men than in women of the same age. Obesity is not listed as a risk factor because it operates through other risk factors that are included (hypertension, hyperlipidemia, and decreased HDL cholesterol, as well as diabetes mellitus, which is treated as a CHD equivalent—see section II.12.b), but it should be considered a target for intervention. Physical inactivity is not listed as a risk factor to modify treatment goals for LDL cholesterol, but it too should be considered a target for intervention, and physical activity is recommended as desirable for everyone. High risk due to CHD or its equivalents is addressed directly in the algorithm.

* Confirmed by measurements on several occasions.

† If the HDL-cholesterol level is ≥60 mg/dL, subtract one risk factor (because high HDL-cholesterol levels decrease CHD risk).

a. Modifiable risk factors

1) Hypertension

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI 1997; Joint National Committee . . . 1997) defines categorical hypertension as a blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic or current use of antihypertensive treatment. Numerous observational studies have demonstrated unequivocally a powerful association of high blood pressure with risk for CHD (MacMahon 1990; Selmer 1992; Stamler 1993; Staessen 1993; Franklin 1999; van den Hoogen 2000). This association holds for men and women and younger and older persons. Even below categorical hypertension, subjects with high-normal blood pressure (130–139 mmHg systolic and/or 85–89 mmHg diastolic) are at increased risk for CHD compared with those with optimal values (Rodgers and MacMahon, 1999; Vasan et al., 1999). Clinical trials have established that blood pressure reduction in people with hypertension reduces risk for a variety of blood pressure-related endpoints including CHD (Cutler 1995). This is true even for older people with isolated

systolic hypertension (SHEP Cooperative Research Group 1991; Staessen et al., 1997). Following the approach taken in ATP II (National Cholesterol Education Program 1993; 1994), JNC VI (JNC VI; Joint National Committee . . . 1997) employed the level of blood pressure and the concomitant presence of risk factors, coexisting cardiovascular disease (CVD), or evidence of target-organ damage to classify blood pressure severity and to guide treatment. Hypertension and high serum cholesterol often occur concomitantly (Working Group . . . 1991; Meigs et al., 1997). Approaches to their joint management are considered in more detail under section VII.6.

***Evidence statements**: Hypertension is a major, independent risk factor for CHD (A2, B1, C1). Treatment of hypertension does not remove all of the CHD risk accompanying elevated blood pressure (A2, B1).*
***Recommendation:** Elevated blood pressure is a risk factor that should modify goals of LDL-lowering therapy in primary prevention (Table II.4–2). Treated hypertension should also count as a risk factor for setting goals of LDL cholesterol in primary prevention. Hypertension should be treated in all affected people according to JNC guidelines.*

2) Cigarette smoking

Cigarette smoking has been established as a powerful contributor to risk for CHD and other forms of CVD (Doll and Peto, 1976; Doll et al., 1980; Kannel et al., 1986; Colditz et al., 1988; Wolf et al., 1988; Government Printing Office 1989; U.S. Surgeon General 1989; Willet 1987; LaCroix 1991; McBride 1992; Jonas et al., 1992; Pyörälä et al., 1994). The relationship of smoking to CVD risk is dose dependent and observed in men and women. Observational data suggest that smoking cessation reduces the risk for CVD events and that the decline in risk begins within months after quitting (U.S. Surgeon General 1990). Randomized clinical trials of smoking cessation in primary prevention settings have revealed substantial reductions in risk for cardiac events in those who quit (Hjermann et al., 1981; Rose et al., 1982; Multiple Risk Factor Intervention Trial Research Group 1982). Cigarette smoking features prominently in the risk assessment component of ATP III because of the CVD risks associated with it and the substantial benefits to be derived from smoking cessation. Moreover, smokers benefit as much, if not more, from LDL-lowering therapy as do nonsmokers (Table II.2–3).

***Evidence statements:** Cigarette smoking is a strong, independent risk factor for CHD (C1). Smoking cessation is accompanied by a reduction in CHD risk (C1).*
***Recommendation:** Prevention of smoking and smoking cessation should receive prime emphasis in the clinical strategy to reduce CHD risk.*

3) Diabetes

Diabetes is defined as a fasting blood glucose of 126 mg/dL or greater (Gavin et al., 1998). Risk for all forms of CVD, including CHD is increased substantially with type 1 and type 2 diabetes mellitus (Kannel and McGee, 1979a,b; Wingard and Barrett-Connor, 1995; Pyörälä et al., 1987; Bierman 1992). Furthermore, the mortality rate in diabetic subjects who have experienced CHD

is much higher than in non-diabetic subjects (Abbott et al., 1988; Herlitz et al., 1992; Miettinen et al., 1998). The increase in risk attributed to hyperglycemia per se is independent of the overweight/obesity and dyslipidemia commonly observed in persons with diabetes. Tighter glycemic control reduces risk for microvascular complications of diabetes such as renal impairment and retinopathy (Diabetes Control and Complications Trial Research Group 1993; The UK Prospective Diabetes Study Group 1998a,c). Thus far, however, improved glucose control in diabetic people has not been definitively shown to reduce macrovascular disease (CHD), although a trend toward benefit has been observed (Diabetes Control and Complications Trial Research Group 1993; The UK Prospective Diabetes Study Group 1998a,c). Importantly, management of other risk factors effectively reduces the incidence of major coronary events in persons with diabetes. This has been shown for tight blood pressure control (the UK Prospective Diabetes Study Group 1998b,d). Analyses of diabetic subgroups within large placebo-controlled trials of cholesterol- and triglyceride-lowering therapy have indicated that the benefits of treatment are comparable among diabetics and non-diabetics (Pyörälä et al., 1997; Haffner et al., 1999a; Goldberg et al., 1998; The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group 1998; Downs et al., 1998; Hoogwerf et al., 1999b; Koskinen et al., 1992; Rubins et al., 1999) (see also Table II.2–3).

A growing body of literature reveals that higher-risk people with diabetes carry an absolute risk for major coronary events similar to that of non-diabetic people with established CHD (Haffner et al., 1998, 2000; Malmberg et al., 2000; Hu et al., 2000). Although some populations with diabetes do not reach this risk level (Simons and Simons, 1998), the very high morbidity and mortality after onset of CHD makes it appropriate to place most people with diabetes in a separate category of risk (see Section II.12.b).

Evidence statements: *Diabetes is a major, independent risk factor for CHD and other forms of CVD (B1). Reducing cholesterol levels in people with diabetes reduces risk for CHD (see Section II.12.b).*
Recommendation: *The presence of diabetes should modify treatment goals for LDL cholesterol. Because of growing evidence that many people with diabetes carry a risk for CHD similar to that of people with established CHD, diabetes should be removed from the list of other risk factors that modify LDL-cholesterol goals. Instead, diabetes should be treated as a separate category of higher risk (see Section II.12.b).*

4) Overweight/obesity

An estimated 97 million adults in the United States are overweight or obese (National Institutes of Health 1998a,b). *Obesity* is defined as a body mass index (weight in kg divided by the square of height in meters) of $\geq$30 kg/m^2 and *overweight* as 25–29.9 kg/m^2 (National Institutes of Health 1998a,b). Although some people classified as overweight actually have a large muscle mass, most persons with BMIs of 25 to 29.9 kg/m^2 have excess body fat. Overweight and obesity not only predispose to CHD, stroke, and numerous other conditions, they also are associated with a greater all-cause mortality (Hubert et al., 1983; Wilcosky et al., 1990; Manson et al., 1990; Calle et al., 1999). People who are overweight or obese have a high burden of other CHD risk factors including dyslipidemia (high LDL cholesterol, low HDL cholesterol, and high VLDL and

triglycerides) (Olefsky et al., 1974; Grundy et al., 1979; Garrison et al., 1980; Denke et al., 1993; 1994), type 2 diabetes (Hartz et al., 1983; Stern and Haffner, 1986) and hypertension (Berchtold et al., 1981a,b; Blair et al., 1984). Obese individuals who do not yet have these risk factors are at increased risk for developing them. The Framingham Heart Study confirms that obesity is strongly predictive of CHD. Risk for CVD is particularly raised when abdominal obesity is present; *abdominal obesity is defined* by a waist circumference greater than 102 cm (40 inches) in men or 88 cm (35 inches) in women (National Institutes of Health 1998a,b).

Despite the strong association between various indicators of obesity and risk for CHD, ATP III does not list obesity among the risk factors that modify the treatment goals for LDL cholesterol. Much of the risk associated with overweight and obesity appears to be mediated through the major risk factors. The independent component of risk has not been quantified. Furthermore, the prevalence of overweight and obesity in the U.S. population is so high that counting them as risk factors to modify LDL goals would enormously expand the population having multiple risk factors, causing an even greater increase in usage of LDL-lowering drugs than will result from the intensified management of persons with multiple risk factors outlined in ATP III. Instead, ATP III identifies overweight and obesity as direct targets of weight-reduction intervention; this approach will achieve more overall risk reduction than will LDL lowering without an emphasis on weight control.

Evidence statement: *Obesity is a major, modifiable risk factor for CHD (C1). Nevertheless, the incremental risk imparted by obesity independently of accompanying risk factors is uncertain.*
Recommendation: *Obesity should be considered a direct target for clinical intervention rather than an indicator for lipid-modifying drug treatment. Because of the association of obesity with other risk factors, obesity should not be included as a factor influencing treatment goals of LDL cholesterol in primary prevention.*

5) Physical inactivity

Physical inactivity is associated with increased risk for CHD. Conversely, physical activity favorably modifies several risk factors; it has been reported to lower LDL and triglyceride levels, raise HDL cholesterol, improve insulin sensitivity, and lower blood pressure (Blair et al., 1983; King and Kriska, 1992; Helmrich et al., 1991; Haskell et al., 1994). Evidence that physical activity can reduce risk for CHD comes from multiple observational studies (Leon et al., 1987; Ekelund et al., 1988; Blair et al., 1989; Morris et al., 1990; Sandvik et al., 1993; Paffenbarger et al., 1993). Therefore, physical inactivity is widely designated to be a major risk factor for CHD (National Cholesterol Education Program 1993; 1994; Fletcher et al., 1996; U.S. Department of Health and Human Services. Physical activity and health . . . 1996). In ATP III, physical inactivity also is listed as a major modifiable risk factor. The mechanisms whereby physical inactivity raises risk for CHD are not fully understood and are probably multifactorial. Physical inactivity reduces caloric expenditure and probably contributes to obesity and to its associated lipid and nonlipid risk factors (Grundy et al., 1999a), as well as to insulin resistance (Perseghin et al., 1996). Beyond its effects on standard risk factors, physical inactivity may have adverse effects on cardiovascular fitness and function. Many of the adverse effects of a sedentary

lifestyle that raise CHD risk can be inferred from the actions of increased physical activity, which include reduction in insulin resistance, lowering of blood pressure, reducing serum triglycerides, raising HDL cholesterol, and improving cardiovascular risk (U.S. Department of Health and Human Services. Physical activity and health . . . 1996).

Although ATP III specifies physical inactivity as a major modifiable risk factor, it does not list it as a risk factor that modifies LDL-cholesterol goals. Because of the collinearity of physical inactivity with other independent risk factors, there is some confounding between physical inactivity and the risk factors that modify LDL goals. Nonetheless, physical inactivity is designated as a major target of intervention for therapeutic lifestyle changes. Undoubtedly some of the benefit of increased physical activity is mediated through mechanisms other than the measured risk factors. In addition, after setting LDL-cholesterol goals with standard risk factors, a physician can take into account a person's levels of physical activity and fitness when adjusting the intensity of LDL-lowering therapy.

It has been suggested that a history of regular physical activity should count as a "negative risk factor," similarly to high HDL cholesterol. Although regular physical activity undoubtedly reduces baseline risk for CHD and should be encouraged, ATP III does not specifically count it as a negative risk factor for setting the goal level for LDL cholesterol.

Evidence statements: *Physical inactivity is a major, modifiable risk factor for CHD (C1). However, a portion of the increased risk for CHD accompanying physical inactivity can be explained by associated major risk factors (C2). Regardless of mechanism, increased physical activity will reduce risk for CHD (B2, C1).*
Recommendations: *Physical inactivity should be a direct target for clinical intervention. Increased physical activity in accord with a person's overall health status should be encouraged as part of lifestyle therapies to reduce risk for CHD. Patients undergoing clinical cholesterol management should be provided with guidance for safe forms of physical activity that will reduce CHD risk beyond LDL-lowering therapy.* *A history of physical inactivity should not be counted as a risk factor for setting goals for LDL cholesterol in primary prevention. However, clinical judgment can be used to decide whether to intensify LDL-lowering therapy in physically inactive persons, or to reduce intensity of therapy in physically active persons.*

6) Atherogenic diet

Prospective studies in populations show that dietary patterns modify the baseline risk of populations (U.S. Department of Agriculture . . . 2000; Krauss et al., 2000). In high-risk populations, some of the adverse effects of diet composition undoubtedly relate to established risk factors, e.g., effects of high intakes of saturated fatty acids and cholesterol on LDL-cholesterol levels and of high salt intakes on blood pressure. Moreover, dietary patterns appear to influence baseline risk beyond the known risk factors. For example, populations that consume diets high in fruits, vegetables, whole grains, and unsaturated fatty acids appear to be at a lower baseline risk than can be explained by standard risk factors. The particular nutrients that impart

this lower risk have not been adequately defined, but strong candidates include antioxidant nutrients, folic acid, other B-vitamins, omega-3 fatty acids, and other micronutrients (Krauss et al., 2000).

Evidence statements: *An atherogenic diet is a major, modifiable risk factor for CHD (C1). High intakes of saturated fatty acids and cholesterol directly raise LDL-cholesterol concentrations (see Section V.5). Further, certain dietary patterns appear to modify baseline risk for CHD, independently of effects on LDL cholesterol (see Sections V.1, V.4, and V.5.c).*
Recommendation: *Modification of an atherogenic diet should be employed to reduce CHD risk as part of overall therapeutic lifestyle changes for CHD risk reduction (see Section V). However, consumption of an atherogenic diet should not be included among risk factors to modify LDL-cholesterol goals in primary prevention.*

b. Nonmodifiable risk factors

1) Age

Risk for coronary disease increases steeply with advancing age in men and women. At any given level of LDL cholesterol, risk for CHD is higher in older than in younger people (Wilson et al., 1998). The principal reason that risk rises with age is that age is a reflection of the progressive accumulation of coronary atherosclerosis, which in turn reflects the cumulative exposure to atherogenic risk factors, both known and unknown. On average, older persons have more coronary atherosclerosis than do younger persons. Once atherosclerosis develops, the coronary plaque itself becomes a "risk factor" for development of clinical CHD. This is because plaque ruptures produce acute coronary events (unstable angina or myocardial infarction), or when plaques grow large, coronary obstructive symptoms (angina pectoris) occur. Recent clinical trials indicate that older persons benefit from LDL-lowering therapy similarly to middle-aged individuals (Table II.2–3).

Evidence statement: *Advancing age is a major, independent risk factor for CHD (C1).*
Recommendation: *Age should count as a risk factor to modify LDL-cholesterol goals in primary prevention.*

2) Male sex

The rise in absolute risk with aging becomes most clinically significant in men in their mid-forties and in women about the time of the menopause. At any given age men are at greater risk for coronary disease than are women (Wilson et al., 1998). Risk in women lags about 10 to 15 years behind that of men. The reasons for a gender difference in CHD risk are not fully understood. Part of the difference can be explained by the earlier onset of risk factors in men, e.g., elevations of LDL cholesterol and blood pressure, and lower HDL cholesterol. However, the Framingham Heart Study has shown that the differences in absolute risk between the sexes

cannot be explained entirely by standard risk factors. Nonetheless, women respond to LDL-lowering therapy with a reduction in relative risk similarly to men (Table II.2–3).

Evidence statement: *Men have a higher baseline risk for CHD than do women at all ages, except perhaps in the oldest age group (>80 years) (C1).*
Recommendation: *An age cutpoint at which age becomes a risk factor to modify goals for LDL cholesterol should be set lower in men (≥45 years) than in women (≥55 years) in primary prevention (Table II.4–2).*

3) Family history of premature CHD

CHD tends to cluster in families, and a positive family history of premature CHD counts as a risk factor. Several prospective studies (Barrett-Connor and Khaw, 1984; Shea et al., 1984; Conroy et al., 1985; Hopkins et al., 1988; Hunt et al., 1986; Jorde and Williams, 1988; Colditz et al., 1991; Kekalainen et al., 1996; Eaton et al., 1996; Pankow et al., 1997; Bensen et al., 1999; Li et al., 2000; Williams et al., 2001) indicate that a family history of premature CHD is an *independent* risk factor even when other risk factors are taken into account. Relative risk for CHD in first-degree relatives has been reported to range from two to as high as 12 times that of the general population (Slack 1969a; Phillips et al., 1974; Rissanen 1979). Risk increases with the number of primary relatives affected and at younger ages of onset in the probands (Pohjola-Sintonen et al., 1998; Rissanen et al., 1977). The clustering of CHD risk in families most closely resembles diseases of polygenic origin and does not follow a Mendelian recessive or dominant pattern that suggests a single gene locus (Siegmund et al., 1998). Among primary relatives, it appears that siblings of probands have the highest relative risk, probably due to shared sociocultural environment, exposures, and genetics. Many prospective cohort and case-control investigations, including the recent Atherosclerosis Risk In Communities Study (ARIC) in four U.S. communities, show this risk to be independent of known risk factors (Bensen et al., 1999; Sharrett et al., 1999). Many risk factors are under genetic control (e.g., blood pressure, lipids and lipoproteins, Lp(a), and obesity), but they account for only a portion of the aggregation of CHD seen in families (Snowden et al., 1982; Khaw and Barrett-Connor, 1986). While family history is immutable, a large number of modifiable risk factors are found in people with a history of premature CHD in a first degree relative (Becker et al., 1988; 1998). This has been demonstrated in both genders and in most races. The Framingham Heart Study family history analysis does not demonstrate sufficient incremental risk for family history to be included in risk assessment equations. Nonetheless, a body of compelling case-control and cohort studies has found family history to be independently associated with higher risk status. The variance across studies depends on the way in which family history is assessed. In the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study and in the Newcastle Family History Study, self-report of a family history of premature CHD in a first degree relative has been found to be reasonably accurate with sensitivity above 80 percent and specificity about 90 percent (Silberberg et al., 1998a,b; Bensen et al., 1999).

Evidence statements: *A positive family history for CHD in a first-degree relative (parent, sibling, or offspring) is a major risk factor for CHD. Often a positive family history is associated with a high prevalence of modifiable risk factors (C1); however, a positive family history carries excess risk beyond standard measurements of risk factors (C1). Risk for CHD is higher the younger the age of onset in the affected family member and the greater the number of affected first degree relatives (C1).*

Recommendation: *The presence and age of onset of CHD in all first-degree relatives should be assessed. The family history should be considered positive for premature CHD if clinical CHD or sudden death can be documented in first degree male relatives 55 years of age and younger and in first degree female relatives 65 years of age or younger. Because a positive family history of premature CHD is immutable but bears information about the risk for CHD and the probability of having modifiable risk factors, it should serve as a factor in making treatment decisions relative to setting and reaching LDL-cholesterol goals in primary prevention (Table II.4–2).*

5. Emerging risk factors

The major risk factors listed in Table II.4–2, along with elevated LDL cholesterol, are powerfully associated with the development of CHD. Although several of them are directly atherogenic, their power to predict CHD is still limited. Most of the *excess risk* for CHD can be explained by the major risk factors; this is shown by the very low risk in persons who have optimal levels of all of these risk factors (see Primary Prevention [Section II.7]). Nonetheless, when major risk factors are present, they account for only about half of the *variability* in CHD risk in the U.S. population; other factors, yet to be identified, seemingly influence how much the major risk factors affect absolute CHD risk. Consequently there has been intensive research to identify new risk factors that will enhance predictive power in individuals. These newer factors can be called *emerging risk factors.* For present purposes, these can be conveniently divided into three categories: lipid risk factors, nonlipid risk factors, and subclinical atherosclerotic disease (see below).

To determine the clinical significance of the emerging risk factors, they must be evaluated against the following criteria used to identify the major risk factors:

- Significant predictive power that is independent of the other major risk factors
- A relatively high prevalence in the population (justifying routine measurement in risk assessment)
- Laboratory or clinical measurement must be widely available, well standardized, inexpensive, have accepted population-reference values, and be relatively stable biologically
- Preferably, but not necessarily, modification of the risk factor in clinical trials will have shown reduction in risk

In the discussion to follow, the *emerging risk factors* are evaluated against these criteria. Even when a factor does not qualify as a major risk factor for routine measurement, its association

with CHD risk deserves some consideration. A review of the key literature is required to determine whether the putative risk factor deserves to be elevated to the level of a major risk factor, and if not, whether it can still be used in selected persons as an adjunct to risk assessment. Even if neither is the case, the risk factor often remains a direct target of therapy, unrelated to modifying LDL-cholesterol goals. If the emerging risk factor is a lipid parameter, its treatment will be considered in more detail elsewhere in this report. If it is a nonlipid risk factor, the reader will be referred to other sources for information on therapy.

A foundation of ATP III is that the major risk factors define absolute risk and thereby modify LDL-cholesterol goals. An initial assessment of risk is made on the basis of these risk factors before any consideration is given to whether emerging risk factors should influence goals or therapies. The same reasoning holds for underlying risk factors: obesity, physical inactivity, and atherogenic diet. On the other hand, ATP III does not discount the influence of underlying or emerging risk factors. *They can be taken into consideration according to clinical judgment as optional modifiers of therapy, but they should be used only as an adjunct to adjust the estimate of absolute risk status obtained with the major risk factors.*

a. Emerging lipid risk factors

1) Triglycerides

Elevated serum triglycerides have long been considered a risk factor by some investigators. The status of triglycerides as a risk predictor is reviewed in other sections of this report (Sections II.3.a and VII). Two questions about triglycerides persist: (a) whether they constitute an independent risk factor for CHD and (b) whether they should be a direct target for therapy. Although recent data point to some independence in risk prediction, their close association with other lipid risk factors (remnant lipoproteins, small LDL, low HDL cholesterol) and nonlipid risk factors makes the issue of their "independence" open to considerable question. In this report, elevated triglycerides are viewed as a marker for other lipid and nonlipid risk factors that themselves raise risk; however, elevated triglycerides per se are not designated a major risk factor to modify goals for LDL cholesterol. Nonetheless, ATP III gives increased weight to elevated triglycerides in cholesterol management in two ways: (a) as a marker for atherogenic remnant lipoproteins and (b) as a marker for other lipid and nonlipid risk factors in the metabolic syndrome (see Section II.6). The former leads to non-HDL cholesterol as a secondary target of therapy when triglycerides are high, whereas the latter calls for more intensive lifestyle therapies (see Section V).

2) Lipoprotein remnants

Many lines of evidence point to the atherogenic potential of lipoprotein remnants (see Section II.3.a.2). Although no single finding confirms remnant lipoproteins as an independent risk factor, circumstantial evidence is strong. Lipoproteins called beta-VLDL, which are apolipoprotein E-enriched remnants and are typical of dysbetalipoproteinemia, almost certainly are atherogenic, because dysbetalipoproteinemia is accompanied by increased risk for CHD (see Section VII). High serum levels of lipoproteins enriched in apolipoprotein CIII, another form of VLDL remnants, appear to be atherogenic as well (Hodis et al., 1994; Koren et al., 1996; Alaupovic et al., 1997; Thompson 1998; Sacks et al., 2000a). Several assays are available for

identification and measurement of remnant lipoproteins; these include ultracentrifugation, electrophoresis, and immunological techniques. Remnant-like particles (RLP) measured immunologically appear to be a promising risk predictor (Leary et al., 1998; McNamara et al., 1998; Devaraj et al., 1998; Masuoka et al., 2000). Even so, prospective studies relating various remnant measures to CHD risk are limited, and measurement with specific assays cannot be recommended for routine practice. Nonetheless, as discussed earlier (see Section II.3.a), ATP III identifies elevated VLDL cholesterol as the surrogate for elevated atherogenic remnants in persons with triglycerides ≥200 mg/dL.

3) Lipoprotein (a)

Several studies (Moliterno et al., 1993; Stubbs et al., 1998; Budde et al., 1994; Seman et al., 1999) report a strong association between Lp(a) levels and CHD risk. Indeed, a recent meta-analysis of reported prospective studies supports an independent predictive power for elevated Lp(a) (Danesh et al., 2000). In addition, concomitant elevations of Lp(a) and LDL cholesterol have been reported to have synergy in elevating risk in both men and women with hypercholesterolemia. On the basis of these studies, some authorities hold that an elevation of Lp(a) is an independent risk factor for CHD. It must be noted nonetheless that several prospective studies (Moliterno et al., 1995; Nishino et al., 2000) do not confirm independent prediction. Of note, Lp(a) levels are higher in African Americans than in Caucasians, but an increased risk for CHD associated with higher Lp(a) levels in African Americans has not been documented (Moliterno et al., 1995). Thus, the quantitative contribution of elevated Lp(a) to CHD risk beyond the major risk factors is uncertain. This uncertainty extends both to individuals and populations; in the latter, the frequency of elevated Lp(a) is not as high as for the major risk factors.

Moreover, issues related to measurement of Lp(a) in clinical practice have not been fully resolved (Marcovina and Koschinsky, 1998; Marcovina et al., 1999). Measurement of Lp(a) is made by immunological methods, and standardized methods are available only in a few reference laboratories. Population reference levels are available from these laboratories, but they are not widely available in clinical practice. Accurate methodology has not yet been established in most clinical chemistry laboratories; samples generally must be sent to special laboratories for measurement. As a result, extra expense in measurement is required. Serum Lp(a) is relatively resistant to therapeutic lowering. Statin drugs are ineffective. Among currently available drugs, only nicotinic acid reduces Lp(a) concentrations, and only moderately (Carlson et al., 1989; Angelin 1997). In postmenopausal women, estrogen therapy also causes some reduction in Lp(a) concentrations (Su et al., 1998). Although these therapies typically lower elevated Lp(a) levels, they have not been widely adopted. At present no clinical trial evidence supports a benefit from lowering Lp(a) levels with particular agents.

Despite limitations in measurement and therapy, some authorities believe that Lp(a) measurement is a useful addition to the major risk factors for identifying persons at still higher risk than revealed by those factors. According to advocates for Lp(a), the option of measurement is best reserved for persons with a strong family history of premature CHD or those with genetic causes of hypercholesterolemia, such as familial hypercholesterolemia (Marcovina and Koschinsky, 1998; Marcovina et al., 1999). An elevated Lp(a) thus presents the option to raise a person's risk to a higher level. For example, if a person has a high LDL cholesterol and only one

other risk factor, the finding of a high Lp(a) could count as a second risk factor to justify a lower goal for LDL cholesterol. ATP III did not find strong evidence to support this approach, but accepts it as an option for selected persons.

4) Small LDL particles

One component of atherogenic dyslipidemia is small LDL particles. They are formed in large part, although not exclusively, as a response to elevations of triglycerides. Their presence is associated with an increased risk for CHD (Austin et al., 1990; Miller et al., 1996; Gardner et al., 1996); however, the extent to which they predict CHD independently of other risk factors is unresolved (Mykkanen et al., 1999). Moreover, standard and inexpensive methodologies are not available for their measurement. For these reasons, ATP III does not recommend measurement of small LDL particles in routine practice. If the clinical decision is made to detect and measure small LDL, their presence is best used as an indicator for atherogenic dyslipidemia and the metabolic syndrome. Their elevation also supports intensified therapeutic lifestyle changes. If small LDL particles accompany elevated triglycerides or low HDL cholesterol in high-risk persons, consideration can be given to using nicotinic acid or fibric acid as components of lipid-lowering therapy. Nonetheless, LDL cholesterol remains the primary target of treatment in persons with small LDL particles.

5) HDL subspecies

HDL comprises several components and subfractions that also have been related to CHD risk. While HDL cholesterol is the risk indicator most often used, HDL subfractions (LpAI and LpAI/AII and/or HDL_3 and HDL_2) have also been used for risk prediction. Although small studies suggest greater predictive power of one or another HDL component, their superiority over HDL cholesterol has not been demonstrated in large, prospective studies. Moreover, measures of HDL subspecies are not readily available in clinical practice. Consequently, ATP III does not recommend the routine measurement of HDL subspecies in CHD risk assessment.

6) Apolipoproteins

a) Apolipoprotein B

Apolipoprotein B is a potential marker for all atherogenic lipoproteins. It has been proposed as an alternative to LDL cholesterol as a risk factor (see Section II.3.b). Limited epidemiological and clinical trial evidence supports its superiority over LDL cholesterol in risk prediction (Rader et al., 1994; Bloch and Couderc, 1998). Nonetheless, the body of evidence in favor of apolipoprotein B has not been developed sufficiently to justify replacing LDL cholesterol, which itself is a powerful independent predictor of CHD (see Section II.2). In addition, from the viewpoint of ATP III, the question is whether apolipoprotein B is preferred as a target of therapy, not as a factor in risk assessment. Although LDL cholesterol and apolipoprotein B are highly correlated in persons with normal triglyceride levels, the apolipoprotein B level typically is disproportionately higher in persons with hypertriglyceridemia. ATP III takes this difference into account and sets a secondary target, non-HDL cholesterol, in persons with hypertriglyceridemia. Non-HDL cholesterol is significantly correlated with apolipoprotein B and can serve as a "surrogate" for it. The non-HDL-cholesterol measure is readily available in clinical practice,

whereas standardized apolipoprotein B measures are not widely available, and in any case, would add expense beyond routine lipoprotein analysis.

b) Apolipoprotein AI

Apolipoprotein AI is carried in HDL, and it is usually low when HDL is reduced. A low apolipoprotein AI thus is associated with increased risk for CHD, but not independently of low HDL. Whether it has independent predictive power beyond HDL cholesterol is uncertain. In any case, standardized methodology for estimating apolipoprotein AI is not widely available. Its measurement thus is not recommended for routine risk assessment in ATP III.

7) Total cholesterol/HDL-cholesterol ratio

Many studies show that the total cholesterol/HDL-cholesterol ratio is a powerful predictor of CHD risk. Some investigators (Hong et al., 1991; Castelli et al., 1992; Kinosian et al., 1995; Criqui and Golomb, 1998) propose that this "cholesterol ratio" is a simple approach for lipid risk assessment. This ratio reflects two powerful components of risk. A high total cholesterol is a marker for atherogenic lipoproteins, whereas a low HDL cholesterol correlates with the multiple risk factors of the metabolic syndrome and probably imparts some independent risk. In fact, however, the total cholesterol/HDL-cholesterol ratio is subsumed in the Framingham global risk equations that are the basis of the 10-year risk assessment used in ATP III. In this way, ATP III incorporates cholesterol ratios into risk assessment. If risk assessment is done using Framingham risk factors as continuous variables (e.g., by risk equations), then the ratio is essentially incorporated. If risk assessment is made using total cholesterol and HDL cholesterol in graded, incremental steps (see Section III), then the ratio is applied approximately. Regardless, ATP III does not define the total cholesterol/HDL-cholesterol ratio as a specified lipid target of therapy. Instead, LDL cholesterol is retained as the primary target of lipid-lowering therapy. Nor is the total cholesterol/HDL-cholesterol ratio recommended as a secondary target of therapy. Treatment of ratios will divert priority from specific lipoprotein fractions as targets of therapy.

b. Emerging nonlipid risk factors

1) Homocysteine

Elevations of serum homocysteine are positively correlated with risk for CHD (Kang et al., 1992; Refsum et al., 1998; Boushey et al., 1995; Malinow et al., 1999; Stehouwer et al., 1998; Folsom et al., 1998; Whincup et al., 1999; Bostom et al., 1999; Giles et al., 2000). The mechanism of the link between homocysteine and CHD is not well understood, although persons with inherited forms of severe homocysteinemia have premature vascular injury and atherosclerosis. In any case, the strength of association between homocysteine and CHD is not as great as that for the major risk factors. Moreover, an elevation of homocysteine is not as common as that of the major risk factors. For these reasons, ATP III does not list elevated homocysteine as a major risk factor to modify LDL-cholesterol goals.

Even though elevated homocyteine is not classified as a major risk factor, some investigators hold that the association with CHD is strong enough to make it a direct target of therapy. The available intervention for elevated homocysteine is dietary folic acid, perhaps combined with

other B vitamins (B6 and B12) (Malinow et al., 1999). Measurement of homocysteine is an option favored by some authorities, with the aim of treating with supplemental B vitamins. Others, however, contend that measurement of homocysteine adds little to risk reduction provided that persons are consuming recommended dietary allowances of folic acid. Several clinical trials are underway to test whether homocysteine lowering will reduce CHD risk (Clark and Collins, 1998). It had been predicted that the recent institution of folate fortification of foods would reduce average levels of homocysteine in the U.S. population (Tucker et al., 1996a,b). Recent data show that this has occurred (Jacques et al., 1999). Substantial increases in serum folate in young women have also been documented (Centers for Disease Control and Prevention 2000).

ATP III does not recommend routine measurement of homocysteine as part of risk assessment to modify LDL-cholesterol goals for primary prevention. This lack of recommendation is based on uncertainty about the strength of the relation between homocysteine and CHD, a lack of clinical trials showing that supplemental B vitamins will reduce risk for CHD, and the relatively low prevalence of elevated homocysteine in the U.S. population. Measurement of homocysteine nonetheless remains an option in selected cases, e.g., with a strong family history of premature CHD in an otherwise low-risk patient. If elevated, the clinical approach favored by ATP III is to determine vitamin B12 level and, if this is normal, to ensure adequate folate intake rather than modifying the LDL-cholesterol goal.

2) Thrombogenic/hemostatic factors

Thrombosis plays a key role in acute coronary syndromes, including myocardial infarction (Fuster and Lewis, 1994). Both platelets and coagulation factors are involved in the thrombotic process. Although the precise hemostatic or prothrombotic mechanisms that predispose to myocardial infarction have not been worked out, the evidence that aspirin and other antiplatelet therapy can reduce risk is compelling and suggests a role for platelet hyperaggregability (Hennekens et al., 1997; Creager 1998; Hansson et al., 1998). Another hemostatic factor associated with CHD risk is fibrinogen (Ernst 1994; Meade 1995; Kannel 1997; Montalescot et al., 1998). A high fibrinogen level associates significantly with increased risk for coronary events, independent of cholesterol level; and conversely, a low fibrinogen level indicates a reduced risk, even in the presence of high total cholesterol levels. Other hemostatic factors that have been found to be associated with increased coronary risk include activated factor VII, plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA), von Willebrand factor, factor V Leiden, protein C, and antithrombin III. Studies have shown that some of these prothrombotic factors are elevated as a component of the metabolic syndrome.

ATP III does not recommend measurement of prothrombotic factors as part of routine assessment of CHD risk. The strength of the association between any of these factors and CHD risk has not been defined. Specific therapeutic interventions, other than aspirin or warfarin therapy, are not available in clinical practice. Clinical trials have not been carried out that target specific prothrombotic factors. Laboratory measurements for prothrombotic factors are not widely available, nor have they been standardized. This said, it is worth noting that the metabolic syndrome is often accompanied by a prothrombotic state, and life-habit intervention to reverse the metabolic syndrome reduces serum levels of prothrombotic factors.

3) Inflammatory markers

The increasing recognition that atherosclerosis involves a chronic inflammatory process has brought greater attention to arterial "inflammation" as a risk factor for major coronary events. In fact, recent reports indicate that serum inflammatory markers, such as C-reactive protein (CRP), carry predictive power for coronary events (Tracy et al., 1997a; Ridker et al., 1998a,b; 1999; 2000; Koenig et al., 1999). High sensitivity (hs) CRP appears to be the most reliable inflammatory marker available at present. Cigarette smoking, which apparently promotes arterial inflammation and predisposes to major coronary events, is associated with higher levels of CRP (Tracy et al., 1997b). Because of the growing evidence that inflammation within coronary plaques predisposes to plaque rupture, one theory holds that an elevation of hs-CRP reflects the presence of "unstable" plaques. The recent observations that obesity and the metabolic syndrome are commonly accompanied by increases in CRP also suggest a close link between metabolic derangement and inflammation (Visser et al., 1999; Ford 1999; Cook et al., 2000). Although adverse metabolism could activate immune mechanisms and predispose to major coronary events, some investigations suggest that chronic, low-grade infections of the arterial wall accelerate atherogenesis and lead to CHD. Infectious agents that have been implicated are Chlamydia pneumoniae and cytomegalovirus.

ATP III does not recommend routine measurement of inflammatory markers for the purpose of modifying LDL-cholesterol goals in primary prevention. A growing body of literature nonetheless suggests that inflammatory markers such as hs-CRP carry some independent predictive power beyond lipid risk factors (Ridker et al., 2000). The extent to which they provide extra prediction beyond all the major risk factors combined is uncertain. Nonetheless, in the opinion of some investigators (Ridker et al., 2000), in persons with elevated hs-CRP, consideration can be given to more aggressively lowering LDL-cholesterol levels than indicated by the goals set by the major risk factors in ATP III.

4) Impaired fasting glucose

A common metabolic abnormality in the metabolic syndrome is an impaired fasting glucose (glucose 100–125 mg/dL). According to the Framingham Heart Study, the association between elevated plasma glucose and CHD risk is a continuous variable; some investigators thus view impaired fasting glucose to be an independent risk factor (Meigs et al., 1998; 2000). However, to other researchers, the strong association between impaired fasting glucose and other risk factors of the metabolic syndrome casts doubt on the independent predictive power of impaired fasting glucose (Fontbonne and Eschwege, 1991; Haffner 1997; Laakso and Lehto, 1998; Gerstein et al., 1999). Moreover, at present, impaired fasting glucose cannot be considered a direct target for drug therapy, although weight reduction and increased physical activity will often correct it. Thus, ATP III identifies impaired fasting glucose as one component of the metabolic syndrome that signifies the need for more intensive lifestyle therapies, i.e., weight reduction and increased physical activity. However, its presence does not place a person in the same high-risk category as does overt diabetes; neither does it count as a risk factor to modify the LDL-cholesterol goal.

c. Subclinical atherosclerotic disease

A large body of data indicates that persons with advanced subclinical coronary atherosclerosis are at greater risk for major coronary events than are persons with less severe atherosclerosis. Although the precise relationship between subclinical atherosclerotic disease and CHD risk has not been defined, subclinical disease must be classified as an emerging risk factor. The American Heart Association recently held a conference (Prevention Conference V) to assess the current status of subclinical atherosclerosis as a predictor of major coronary events (Smith et al., 2000a,b; Grundy et al., 2000; Greenland et al., 2000). The major findings of this report represent current understanding of the predictive power of subclinical disease. The conclusions of the Prevention Conference V report are represented in the position of ATP III on subclinical atherosclerotic disease.

1) Ankle-brachial blood pressure index (ABI)

The ABI is a simple, inexpensive, noninvasive test to confirm the clinical suspicion of lower extremity peripheral arterial disease (PAD). It is performed by measuring the systolic blood pressure (by Doppler probe) in brachial, posterior tibial, and dorsalis pedis arteries. An ABI of <0.9, found in either leg, is diagnostic of PAD, and prospective studies indicate that risk for major coronary events is in the range of that of persons with established CHD (Criqui et al., 1985; Criqui et al., 1992). The test is most likely to be positive in persons over age 50 who have other risk factors. A strong case can be made that a positive ABI essentially constitutes a *diagnosis* of PAD. Consequently the ABI can be considered a diagnostic test to identify persons at high risk for CHD (see Section II.12.a).

2) Tests for myocardial ischemia

Tests available in this category include standardized exercise electrocardiogram (ECG) testing, myocardial perfusion imaging, and stress echocardiography. Exercise ECG testing has been extensively studied. A positive exercise ECG in asymptomatic, middle-aged men with traditional risk factors carries independent predictive power for major coronary events; thus, exercise testing carries the potential to identify middle-aged men who are at higher risk than revealed by the major risk factors. Consequently a positive test could call for more aggressive risk-reduction therapies. The same predictive power apparently does not hold for young adults and middle-aged or older women; a "positive" test is much less predictive of major coronary events. In these groups, the likelihood of inappropriate application of aggressive preventive measures is increased. Myocardial perfusion imaging and stress echocardiography have been less extensively evaluated for their predictive power, although they appear to contain independent prognostic information. Certainly a positive perfusion imaging result obtained in middle-aged men with multiple risk factors and men ≥45 years with a strong family history of CHD is strongly indicative of obstructive coronary atherosclerosis and carries a high risk for acute coronary syndromes. The decision to employ perfusion imaging in appropriately selected persons depends on clinical judgment. The expense of the test and its low yield of positive outcomes makes it unsuitable for routine risk assessment in asymptomatic persons, but does not exclude its clinical utility in selected persons. In ATP III, the presence of myocardial ischemia appropriately identified by stress testing qualifies as a diagnosis of CHD.

3) Tests for atherosclerotic plaque burden

a) Carotid intimal medial thickening

One test in this category is *carotid sonography* used to measure intimal medial thickness (IMT) of the carotid arteries (Greenland et al., 2000). The extent of carotid atherosclerosis correlates positively with the severity of coronary atherosclerosis. Furthermore, recent studies show that severity of IMT independently correlates with risk for major coronary events (Chambless et al., 1997; Hodis et al., 1998; O'Leary et al., 1999; Greenland et al., 2000). Thus, measurement of carotid IMT theoretically could be used as an adjunct in CHD risk assessment. For instance, the finding of an elevated carotid IMT (e.g., 75th percentile for age and sex) could elevate a person with multiple risk factors to a higher risk category. However, its expense, lack of availability, and difficulties with standardization preclude a current recommendation for its use in routine risk assessment for the purpose of modifying intensity of LDL-lowering therapy. Even so, if carried out under proper conditions, carotid IMT could be used to identify persons at higher risk than that revealed by the major risk factors alone.

b) Coronary calcium

Another indication of subclinical coronary atherosclerosis is coronary calcium as detected by *electron beam computed tomography (EBCT)* or *spiral CT.* Amounts of coronary calcium correlate positively with coronary plaque burden. Therefore, a high coronary calcium score should carry predictive power for major coronary events (Smith et al., 2000a; Greenland et al., 2000). Several studies indicate that, in persons with multiple risk factors, a concomitantly high coronary calcium score places persons in the range of a CHD risk equivalent (Detrano et al., 1999; Raggi et al., 2000; Arad et al., 2000; Wong et al., 2000; O'Malley et al., 2000). A recent report by the American College of Cardiology/American Heart Association (ACC/AHA) acknowledged the potential power of coronary calcium to predict major coronary events (O'Rourke et al., 2000a,b). At the same time, this report emphasized the limitations of the technique as a tool to diagnose obstructive coronary disease for the purpose of coronary revascularization. Despite these limitations, both the Prevention V report and the ACC/AHA report affirmed that use of EBCT for risk prediction can be an option, provided its use is limited to patients referred by physicians. Under these circumstances, when used appropriately, measurement of coronary calcium could be of value for persons whose absolute risk is greater than that revealed by the major risk factors. Thus, a high coronary calcium score in a patient with multiple risk factors is consistent with a still higher risk state.

In accord with recent reports (Smith et al., 2000b; O'Rourke et al., 2000a,b), ATP III does not recommend EBCT for indiscriminate screening for coronary calcium in asymptomatic persons, particularly in persons without multiple risk factors. Its predictive power for persons without multiple risk factors has not been determined in prospective studies. Testing is relatively expensive and not widely available. It should be used primarily as an adjunct to modify risk assessment based on the major risk factors. Only in exceptional cases should it evoke further invasive diagnostic tests and interventions. Despite uncertainties as to the predictive power of coronary calcium, ATP III supports the conclusions of AHA's Prevention Conference V and the ACC/AHA report that high coronary calcium scores signify and confirm increased risk for CHD when persons have multiple risk factors. Therefore, measurement of coronary calcium is an

option for advanced risk assessment in appropriately selected persons, provided the test is ordered by a physician who is familiar with the strengths and weaknesses of noninvasive testing. In persons with multiple risk factors, high coronary calcium scores (e.g., >75th percentile for age and sex) denotes advanced coronary atherosclerosis and provides a rationale for intensified LDL-lowering therapy. Moreover, measurement of coronary calcium is promising for older persons in whom the traditional risk factors lose some of their predictive power (Grundy et al., 1999b). For example, a high coronary calcium score could be used to tip the balance in favor of a decision to introduce LDL-lowering drugs for primary prevention in older persons.

6. Metabolic syndrome

a. Metabolic syndrome as multiple, interrelated factors that raise risk

This syndrome has become increasingly common in the United States. It is characterized by a constellation of metabolic risk factors in one individual (Reaven 1995; Grundy 1999a; Meigs 2000). The root causes of the metabolic syndrome are overweight/obesity, physical inactivity, and genetic factors. The metabolic syndrome is closely associated with a generalized metabolic disorder called *insulin resistance*, in which tissue responsiveness to the normal action of insulin is impaired (Kolaczynski and Caro, 1998; Zimmet et al., 1999; Haffner 1999*).* Some individuals are genetically predisposed to insulin resistance; in these persons, acquired factors (excess body fat and physical inactivity) elicit insulin resistance and the metabolic syndrome. Most persons with insulin resistance have abdominal obesity (Despres 1993; Despres 1998; Bjorntorp 1997). The mechanistic connections between insulin resistance and metabolic risk factors are not fully understood and appear to be complex. Various risk factors have been included in the metabolic syndrome; the following list contains those factors that are generally accepted as being characteristic of this syndrome:

- Abdominal obesity
- Atherogenic dyslipidemia
- Raised blood pressure
- Insulin resistance $\pm$ glucose intolerance
- Prothrombotic state
- Proinflammatory state

Because of the high degree of association of these risk factors in persons with the metabolic syndrome, it has proven difficult to dissect the individual contributions of each factor to CHD risk. However, there is little doubt that this syndrome taken in aggregate enhances the risk for CHD at any given LDL-cholesterol level. From a population viewpoint, the increasing prevalence of the metabolic syndrome threatens to partially reverse the reduction in CHD risk that has resulted from a decline in serum LDL cholesterol levels in the U.S. population, which has occurred over the past three decades. The metabolic syndrome and its associated risk factors have emerged as a coequal partner to cigarette smoking as contributors to premature CHD (Wilson 1998; Assmann et al., 1998b; Eckel and Krauss, 2000; National Institutes of Health 1998a,b; U.S. Department of Health and Human Services. Physical activity and health . . . 1996). In addition, the insulin resistance accompanying the metabolic syndrome is one of the underlying

causes of type 2 diabetes (Groop 1999; Cavaghan et al., 2000). For these reasons, ATP III places increased emphasis on the metabolic syndrome as a risk enhancer.

There are two general approaches to the treatment of the metabolic syndrome. The first strategy modifies root causes, overweight/obesity and physical inactivity, and their closely associated condition, insulin resistance. Weight reduction (Dengel et al., 1998; Ahmad et al., 1997; Su et al., 1995) and increased physical activity (Devlin 1992; Perseghin et al., 1996) both lower insulin resistance and indirectly mitigate the metabolic risk factors. The second approach directly treats the metabolic risk factors—atherogenic dyslipidemia, hypertension, the prothrombotic state, and underlying insulin resistance. At present, most success in clinical practice comes from pharmacological modification of the associated risk factors. However, the greatest potential for management of the syndrome lies in reversing its root causes. ATP III promotes this latter approach, which is a major new initiative for persons entering clinical cholesterol management.

***Evidence statements**: The presence of the metabolic syndrome accentuates the risk accompanying elevated LDL cholesterol (C1). This increase in risk appears to be mediated through multiple risk factors—major and emerging risk factors (C1).*

Clinical trials show that modifying three major components of the metabolic syndrome—atherogenic dyslipidemia (B2), hypertension (A2, B1)[*], and the prothrombotic state (A2, B1[†])—will reduce risk for CHD.

***Recommendations**: Increased emphasis should be placed on therapeutic modification of the metabolic syndrome in persons undergoing LDL-lowering therapy. Primary management of the metabolic syndrome should be to reverse its root causes—overweight/obesity and physical inactivity. In addition, other lipid and nonlipid risk factors associated with the metabolic syndrome should be appropriately treated.*

The presence of the metabolic syndrome provides the option to intensify LDL-lowering therapy after LDL-cholesterol goals are set with the major risk factors. Primary emphasis nonetheless should be given to modifying the underlying risk factors (overweight/obesity and physical inactivity) and other risk factors associated with the metabolic syndrome.

* See JNC VI. (JNC VI 1997; Joint National Committee . . . 1997).

† See results of meta-analysis of aspirin trials.

b. Diagnosis of metabolic syndrome

There are no well-accepted criteria for the diagnosis of the metabolic syndrome. Nonetheless, many persons seen in clinical practice are readily recognized as having multiple metabolic risk factors. Most persons with the metabolic syndrome are overweight or obese; clinical studies have noted a high correlation between abdominal obesity and the risk factors characteristic of the metabolic syndrome (Bjorntorp 1997; Despres 1993; Okosun et al., 2000; Bjorntorp 1992). For example, closely associated with abdominal obesity is an elevation of serum triglycerides (Mekki et al., 1999; Bodkin et al., 1993; Julien et al., 1997). The elevation can be either borderline high (150–199 mg/dL) or high ($\geq$200 mg/dL). A higher triglyceride level is usually accompanied by lower HDL-cholesterol concentrations (Phillips et al., 1981; Schaefer et al., 1988). HDL-

cholesterol levels <40 mg/dL occur commonly in men with insulin resistance (Karhapaa et al., 1994). Further, moderate (marginal) reductions of HDL-cholesterol levels are observed commonly in women with the syndrome (Nilsson et al., 2000; Vanhala et al., 1997); thus for women, HDL cholesterol <50 mg/dL counts as one indicator in the diagnosis of the metabolic syndrome. A moderately strong association exists between insulin resistance and hypertension (Lind et al., 1995; Lender et al., 1997; Landsberg 1999). Insulin resistance also is associated with high-normal blood pressure (Dyer et al., 1999; Falkner et al., 1999).

Impaired fasting glucose (110–125 mg/dL) usually is an indicator of insulin resistance and is frequently accompanied by other metabolic risk factors (Tripathy et al., 2000; Haffner et al., 1996); measurement of fasting glucose in overweight and obese persons is a reasonable option (National Institutes of Health 1998a,b). A portion of persons with impaired fasting glucose will eventually develop type 2 diabetes (Edelstein et al., 1997; Lindahl et al., 1999), which further enhances risk for CHD. Type 2 diabetes is the epitome of the metabolic syndrome. Other components of the metabolic syndrome (insulin resistance, proinflammatory state, and prothrombotic state) cannot be identified by routine clinical evaluation. However, in the presence of abdominal obesity, they often are present. For present purposes, the metabolic syndrome is identified by the presence of three or more of the components listed in the following table.

Table II.6–1. Clinical Identification of the Metabolic Syndrome*

Risk Factor	Defining Level
Abdominal Obesity Men Women	Waist Circumference† >102 cm (>40 in) >88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol Men Women	 <40 mg/dL <50 mg/dL
Blood pressure	≥130/85 mmHg
Fasting glucose	110–125 mg/dL

* The ATP III panel did not find adequate evidence to recommend routine measurement of insulin resistance (e.g., plasma insulin), proinflammatory state (e.g., high-sensitivity C-reactive protein), or prothrombotic state (e.g., fibrinogen or PAI-1) in the diagnosis of the metabolic syndrome.

† Some male persons can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94–102 cm (37–39 in). Such persons may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

c. Metabolic syndrome as a target of therapy

In persons entering clinical management of elevated LDL cholesterol, the full benefit of risk reduction will be lost if the metabolic syndrome is ignored. To achieve maximal benefit from modification of multiple metabolic risk factors, the underlying insulin resistant state must become a target of therapy. The safest, most effective, and preferred means to reduce insulin resistance is weight reduction in overweight and obese persons and increased physical activity. Both weight control (Dengel et al., 1998; Ahmad et al., 1997; Su et al., 1995) and exercise

(Devlin 1992; Perseghin et al., 1996; Hu et al., 2001; Farrell et al., 1998) reduce insulin resistance and favorably modify the metabolic risk factors. ATP III thus places increased emphasis on the metabolic syndrome and on its favorable modification through changes in life habits.

Drug treatment of several of the individual risk factors of the metabolic syndrome will reduce risk for CHD. The strong trend for benefit of drug treatment of atherogenic dyslipidemia is discussed in Section II.3. Risk reductions by lowering blood pressure with antihypertensive drugs (JNC VI 1997; Joint National Committee . . . 1997) and treating the prothrombotic state with aspirin (Hennekens et al., 1997) are well established. However, lowering serum glucose with drugs has not yet been documented to reduce risk for CHD. Although drugs are available to reduce insulin resistance, there is no clear evidence yet that they will reduce risk for CHD in persons with the metabolic syndrome.

7. Primary prevention: persons without established CHD

a. Scope of primary prevention

Primary prevention aims to prevent new onset CHD. If prevention is delayed until advanced coronary atherosclerosis has developed, the U.S. public will continue to suffer from a heavy burden of CHD. The essential approach to primary prevention is to reduce risk factors for CHD. Waiting until a diagnosis of CHD is made before beginning risk factor reduction will miss the opportunity to prevent CHD in people whose first presentation is sudden cardiac death or disability (deVreede-Swagemakers et al., 1997; Kannel 1985b; Muller et al., 1997; American Heart Association 1998). One-third of people who experience a myocardial infarction will die within 24 hours and many survivors will have serious morbidity including congestive heart failure, angina, arrhythmias, and an increased risk of sudden death (American Heart Association 1998). One-third of all new cardiovascular events occurs in individuals under age 65 (AHA Heart Facts, 1999). These observations argue strongly for primary prevention of CHD.

Elevations of serum LDL cholesterol contribute importantly to the high prevalence of CHD in the United States. International studies find that CHD is uncommon in cultures with low levels of serum cholesterol even when the prevalence of hypertension and cigarette smoking is relatively high (Keys 1980; Grundy et al., 1990; Tunstall-Pedoe et al., 1994). Migration studies reveal that persons who emigrate from low-risk to high-risk cultures show a rise in LDL-cholesterol levels and assume the risk of the new culture (Marmot et al., 1975). Mass elevations of serum LDL cholesterol result from the habitual diet in the United States**,** particularly diets high in saturated fats and cholesterol (Keys et al., 1980; Blackburn 1990; Krauss et al., 1996; 2000; U.S. Department of Agriculture . . . 2000). When these diets are combined with a relatively heavy burden of other CHD risk factors, a high prevalence of premature CHD results.

b. Clinical strategy in primary prevention effort

NCEP supports two complementary approaches to primary prevention: (1) population strategies and (2) clinical strategies (National Cholesterol Education Program 1990; Report of the Expert Panel on Population Strategies . . . 1991). NCEP encourages dietary and other behavioral

interventions for all Americans to reduce the population burden of atherosclerosis. The clinician has the opportunity to bridge the gap between the public health population strategy and clinical primary prevention. The population approach is augmented when physicians reinforce the public health message (see Section V). The clinical approach is needed to identify higher risk persons in whom risk factor modification is more urgently required. It further extends to the identification of relatives of affected persons who also are at higher risk and who need clinical intervention to modify risk factors.

c. Concepts of short-term and long-term prevention

Clinical primary prevention can be categorized into long-term and short-term prevention. Long-term prevention aims to reduce risk for CHD over a lifetime; its goal is to prevent the initiation and progression of coronary atherosclerosis, the underlying cause of CHD. It is directed towards persons who are not in imminent danger of suffering a major coronary event, but instead have a high probability of developing CHD sometime during their lives. Lifetime prevention places priority on modifying adverse life habits that are the underlying causes of risk factors and coronary atherosclerosis. In some persons, however, when risk factors are categorically abnormal drug therapy is required in addition to life-habit changes to reduce long-term risk.

Short-term prevention is designed to reduce risk for new onset CHD, mostly acute coronary syndromes, over the next few years (e.g., $\leq$10 years). It is directed towards persons who in all probability already have advanced coronary atherosclerosis and who are at high risk of suffering acute coronary syndromes. Such higher risk persons deserve more intensive intervention. Modification of life habits remains an important component of risk reduction in the short term, but more persons will require the addition of pharmacological therapy to reduce risk factors than in long-term prevention.

d. Role of LDL lowering in short-term and long-term primary prevention

Several general comments can be made about the role of LDL lowering in short-term and long-term prevention before addressing specific issues in these areas. A broad base of evidence indicates that elevations in LDL cholesterol are a direct cause of atherosclerosis. Long-term elevations of LDL cholesterol lead to a progressive accumulation of coronary atherosclerosis, which is essential to development of clinical CHD. Recent clinical trials demonstrate that LDL-lowering therapy reduces CHD risk in both primary and secondary prevention. In fact, LDL lowering reduces risk even when LDL-cholesterol levels are not categorically high. For this reason, LDL-lowering therapy represents a powerful modality for reducing both short-term and long-term risk.

Persons at higher risk in the short term (i.e., $\leq$10 years) deserve highest priority in clinical intervention. Identification of higher risk persons thus becomes a critical issue. This identification is based largely on algorithms that take into account the interaction of multiple risk factors that raises CHD risk multiplicatively. These short-term risk estimates are less reliable for selection of candidates for long-term prevention in clinical practice. Long-term prevention begins with a fundamental principle: all categorical risk factors should be managed clinically regardless of projected short-term risk. All of the major risk factors for CHD—cigarette

smoking, hypertension, elevated LDL cholesterol, and diabetes—can produce CHD or other cardiovascular disease even in the absence of other risk factors. Each deserves clinical intervention. In the case of LDL cholesterol, a categorical elevation for ATP III is defined as a level ≥160 mg/dL. Many persons with persistent levels of LDL cholesterol in this range will ultimately require LDL-lowering drugs to reduce risk, although therapeutic lifestyle changes are first-line management. For persons with LDL-cholesterol levels ≥160 mg/dL, categorization of absolute risk can help guide the type and intensity of therapy. Furthermore, some persons with lower levels of LDL cholesterol, e.g., 130–159 mg/dL, will nonetheless have a short-term risk high enough to justify LDL-lowering drugs because of other risk factors. Absolute risk assessment will assist in identification of the latter persons.

e. Risk assessment in primary prevention

In accord with the preceding comments, clinical risk assessment has two goals: to identify persons who are at risk for accelerated atherogenesis, and to identify those persons who are at higher risk for experiencing an acute coronary syndrome because of established advanced atherosclerosis. Long-term prevention in clinical practice is designed for the former, whereas short-term prevention is intended for the latter. Short-term risk reduction (i.e., prevention of coronary plaque rupture and acute coronary syndromes) depends almost exclusively on absolute-risk assessment for its selection of persons for intense clinical intervention. For short-term prevention, absolute risk can be estimated by the summed interaction of multiple coronary risk factors.

NCEP originally introduced a simple system of risk assessment that employed counting of categorical risk factors (Table II.4–2). Treatment goals for LDL cholesterol were set according to the number of risk factors. This system represented a blending of the concepts of relative and absolute risk in an effort to effectively institute both long-term and short-term prevention. The major intervention in NCEP recommendations has been lifestyle changes; LDL-lowering drugs were reserved for persons with categorical elevations of LDL cholesterol who were projected to be at highest risk. After release of ATP II, several major clinical trials reported results showing the efficacy and safety of LDL-lowering drugs for primary prevention (as well as for secondary prevention). These reports opened the door to wider use of LDL-lowering drugs, both for short-term and long-term prevention. In particular, there is a growing consensus that higher risk persons should not be denied the proven short-term benefits of LDL-lowering drugs, even when LDL-cholesterol levels are <160 mg/dL. Consequently, the selection of persons for short-term prevention to reduce plaque rupture and acute coronary syndromes has assumed increased importance. Moreover, there has been a growing view that a more quantitative assessment of short-term risk is required for the selection of persons who will benefit most from intensive risk-reduction intervention.

The Framingham Heart Study provides an algorithm for assessing risk for CHD in the short term (≤10 years) (Wilson et al., 1998). This algorithm, which is based on robust risk factors, has been adopted by European cardiovascular societies for their treatment guidelines (Prevention of coronary heart disease in clinical practice, 1998; Wood et al., 1998), the British cardiovascular societies (Joint British recommendations 1998; 2000; Faergeman 1999) and the American Heart Association (Grundy et al., 1999c). In 1999, the National Heart, Lung, and Blood Institute

sponsored a workshop to evaluate the applicability of Framingham risk scores to other population groups in the United States (Grundy et al., 2001a). Framingham projections for "hard" CHD (myocardial infarction and CHD deaths) were found to be similar to those found in other prospective studies in both Caucasian and African American populations in the United States. Comparisons also showed that Framingham scoring led to some overestimation of absolute risk in certain population groups, e.g., Japanese men in Hawaii (Honolulu Heart Program) and Hispanic persons in Puerto Rico (Grundy et al., 2001a). Nonetheless the broad "transportability" of Framingham risk scores within the U.S. population makes it possible for ATP III to employ the Framingham algorithm for quantitative risk assessment to assist in matching intensity of therapy with absolute risk. It must be noted, however, that other published risk assessment algorithms are available (Cullen et al., 1998). All algorithms do not contain the same factors, nor are risk predictions entirely congruent. Moreover, Framingham scoring itself has been undergoing modification over the past few years. Therefore, absolute risk estimation must be viewed as an evolving science. This is particularly the case as emerging risk factors and measures of subclinical atherosclerosis are added to risk assessment algorithms.

The ATP III panel was faced with the need to reconcile its previous method of counting risk factors with the developing field of integrated, "global" risk assessment. There are advantages and disadvantages to each approach. For example, risk factor counting provides continuity with previous ATP guidelines; it allows for a history of detected risk factors to be included in risk assessment; it includes family history of premature CHD; and it provides a focus on the individual risk factors, each of which requires clinical intervention. However, risk factor counting alone also has disadvantages: it does not provide a quantitative estimate of absolute risk in the short term; it does not allow for variability in risk factor level or intensity (i.e., it uses only categorical risk factors); and it may underestimate the progressive impact of advancing age on absolute risk in older persons. Integrated models of risk estimation (e.g., Framingham risk scoring) counter several of these disadvantages. For instance, they give a more quantitative absolute risk prediction for short-term risk; they account for variability in risk factor intensity, including the progressive impact of advancing age on risk; and they can include corrections for the interactions of risk factors. Even so, there are disadvantages or potential disadvantages to quantitative models for risk estimation: they introduce an approach that has not been widely field tested for practicality in clinical practice; they do not account for variability of risk factor level from one clinic visit to another (and no historical information on variable risk factors is included); they require extra steps in risk assessment (either manual or computer-based assessment); they tend to focus primary attention on short-term risk (to the exclusion of long-term risk); their transportability to all populations is uncertain; and there are remaining uncertainties due to competing and evolving risk-assessment models. All of these factors were taken into account in the ATP III choice of risk assessment methods.

The final method chosen attempts to capitalize on the advantages of both approaches. Risk factor counting is retained for initial assessment, but Framingham risk scoring, updated for ATP III (see Section III), is layered over risk factor counting to improve risk estimation for refining decisions about goals, intensity, and types of LDL-lowering therapy in persons with multiple risk factors. In the final analysis, however, ATP III risk assessment allows physicians to begin with either approach; ultimately the two give similar results. The method of risk assessment therefore depends on physician preference. These methods are described in detail in Section III.

f. Primary prevention with lifestyle changes

1) Basis for lifestyle recommendations for primary prevention

A broad base of evidence supports recommendations for lifestyle changes for LDL-lowering therapy in primary prevention.

2) Dietary clinical trials of cholesterol lowering

A sizable number of clinical trials have been carried out to test whether lowering serum cholesterol levels with dietary modification will reduce risk for CHD. Some of these were primary prevention trials (Dayton et al., 1968; Frantz et al., 1989; Miettinen et al., 1972; Hjermann et al., 1981; Multiple Risk Factor Intervention Trial 1976), and others were secondary prevention trials (Ball et al., 1965; Research Committee 1965; Leren 1966). None of these trials provided convincing proof of the efficacy of serum cholesterol lowering by dietary means to reduce CHD risk. Most of the trials, however, showed positive trends. In a meta-analysis of dietary trials, Gordon (1995a,b; 1999) found that dietary lowering of serum cholesterol produces as much CHD risk reduction as do drugs, commensurate with their respective degree of cholesterol lowering.

3) Linkage of public health approach and clinical approach in primary prevention

A strong case exists for the efficacy and safety of primary prevention through lifestyle changes. Primary prevention efforts extend to both public health and clinical arenas. The essential changes in life habits include smoking avoidance or cessation, modifying intakes of foods and nutrients, weight control, and physical activity. Evidence to support each of these changes has been presented in the NCEP Population Report (National Cholesterol Education Program 1990; Report of the Expert Panel on Population Strategies . . . 1991), U.S. Surgeon General's reports on Smoking (U.S. Surgeon General 1990) and on Physical Activity (U.S. Department of Health and Human Services 1996b); the Obesity Clinical Guidelines Report (National Institutes of Health 1998a,b), and Dietary Guidelines for Americans 2000 (U.S. Department of Agriculture . . . 2000). ATP III affirms the validity of lifestyle changes as first-line therapy for primary prevention. It places priority on LDL-lowering modifications because of the identification of LDL cholesterol as the primary target of therapy; however, ATP III also urges the use of a broad approach to lifestyle changes for CHD risk reduction in primary prevention.

g. Effectiveness of LDL-lowering drugs in primary prevention

Clinical trials of cholesterol-lowering drugs support the efficacy of clinical primary prevention in higher risk persons. In the era before statin drugs, several primary prevention trials of cholesterol lowering were carried out with drug intervention (Grundy 2000a). Landmark trials among these were the World Health Organization clofibrate trial (Committee of Principal Investigators 1978), the Helsinki Heart Study gemfibrozil trial (Frick et al., 1987; Huttunen et al., 1991; 1994), and the Lipid Research Clinics cholestyramine trial (Lipid Research Clinics Program 1984a,b). All of these trials of lipid-lowering therapy reduced major coronary events. However, they were underpowered to address the issue of total mortality; hence, in the minds of many, the benefits of lipid modification in primary prevention remained uncertain (Oliver 1981; Muldoon et al., 1990;

Ravnskov 1992). The availability of more efficacious cholesterol-lowering drugs (statins) made it possible to definitively test whether LDL lowering would reduce CHD risk. Two major primary prevention trials with statins were the West of Scotland Coronary Prevention Study (WOSCOPS) (Shepherd et al., 1995) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (Downs et al., 1998). Their results are summarized in Table II.7–1. In both trials, statin therapy significantly reduced relative risk for major coronary events. WOSCOPS also showed a very strong trend towards a reduction in total mortality. In AFCAPS/TexCAPS, the numbers of deaths in both placebo and treatment groups were so small that no conclusions could be drawn about effects of cholesterol-lowering therapy on total mortality; however, no significant adverse effects of statin therapy were detected.

Table II.7–1. Major Primary Prevention Trials with Statins

Study	Persons	Duration	Statin Drug (dose/d)	Baseline LDL-C (mg/dL)	LDL-C Change	Major Coronary Events	Revascu-larization	Coronary Mortality	Total Mortality
WOSCOPS	6595	4.9 yrs	Pravastatin 40 mg	192	-26%*	-31%*	-37%*	-33%*	-22%*
AFCAPS/ TexCAPS	6605	5 yrs	Lovastatin 20/40 mg	150	-25%*	-37%*	-33%*	NS	NS

* Changes significant at p<0.05 or lower.

WOSCOPS and AFCAPS/TexCAPS have important differences that reveal the potential spectrum of use of drugs for primary prevention. WOSCOPS participants, on average, had high LDL-cholesterol levels at baseline, and they often had multiple risk factors. AFCAPS/TexCAPS participants, in contrast, had only borderline high LDL-cholesterol levels and fewer other risk factors, except for relatively low HDL-cholesterol levels. Because of higher LDL cholesterol and more risk factors, WOSCOPS participants had a relatively high absolute risk. AFCAPS/TexCAPS is important because it showed that LDL-lowering therapy in persons with only borderline-high LDL-cholesterol levels produces a large reduction in relative risk. Nevertheless, absolute risk reduction was lower than in WOSCOPS participants, so that more persons had to be treated to receive the benefits of treatment. The implications of these two studies for use of LDL-lowering drugs in primary prevention are considered briefly below.

h. Selection of persons for short-term risk reduction with LDL-lowering drugs

The major reason for using LDL-lowering drugs in short-term, primary prevention is to reduce the likelihood of major coronary events in persons who presumably have advanced coronary atherosclerosis. Primary prevention trials with LDL-lowering drugs provide the rationale for this approach. The most robust primary prevention trial for evaluating benefits of LDL-lowering therapy was WOSCOPS. Its participants generally had elevated LDL cholesterol along with other CHD risk factors. In the WOSCOPS placebo group, 10-year risk for major coronary events (myocardial infarction and CHD death) was approximately 15 percent. Statin therapy reduced this risk by about one-third (Table II.7–1). In AFCAPS/TexCAPS, the estimated 10-year risk for major coronary events in the placebo group was 10.9 percent, but almost half of these events were unstable angina; risk for hard CHD (myocardial infarction + CHD death) was only about 7 percent. Thus, absolute risk in WOSCOPS participants was

approximately twice that of AFCAPS/ TexCAPS participants. Statin therapy in AFCAPS/TexCAPS produced reductions in relative risk similar to those in WOSCOPS; nonetheless, because of lower absolute risk in AFCAPS/TexCAPS, the number needed to treat (NNT) for every event prevented was higher than in WOSCOPS.

In these two primary prevention studies, statin therapy proved to be remarkably safe as well as efficacious. Since safety does not appear to be an issue for short-term risk reduction in primary prevention with LDL-lowering drugs, the determining factor for the lower risk cutpoint for drug recommendation will be cost-effectiveness (see Section II.14). As noted in Section II.14, the lower cutpoint for selection of drug therapy at current prices of LDL-lowering drugs is a risk for myocardial infarction and coronary death of about 1 percent per year (or 10 percent per 10 years). By this criterion many persons entering AFCAPS/TexCAPS were below accepted cost-effectiveness for short-term risk reduction with statins.

It must be emphasized that the ATP III clinical guidelines do not advocate the attainment of LDL goals exclusively through drug therapy. The aim of therapy is to achieve the LDL goals that are set according to absolute risk criteria. ATP III recommendations call for achieving the goals of therapy by the safest and most cost-effective means. Use of dietary therapy to attain the targets of therapy is emphasized, and if drugs are required, cost-effective agents should be used in the lowest doses needed to achieve the recommended goals of therapy.

i. Selection of older persons for short-term, primary prevention

Approximately two-thirds of first major coronary events occur in persons ≥65 years. Many asymptomatic older persons have advanced coronary atherosclerosis. Recent clinical trials have revealed that aggressive LDL-lowering therapy is effective in reducing risk for CHD (see Table II.2–3). Therefore, the prospects for reducing clinical CHD in the United States by intensive LDL lowering are good. To maximize this benefit, LDL-lowering drugs will be needed for many persons at higher risk. However, to fully implement widespread use of LDL-lowering drugs in older populations, several major problems will have to be overcome. For example, the most effective LDL-lowering drugs (statins) are often expensive; at current prices, statin therapy can cost up to $500–$1,500 per year. At present, Medicare does not pay for prescription drugs, and many older Americans do not have other private insurance to cover this high cost. Moreover, techniques to assess absolute risk in older persons are less reliable than for middle-aged persons. In particular, serum cholesterol is less robust as a predictor of CHD events in the elderly than in the middle aged (Psaty et al., 1999). Measurements of subclinical atherosclerosis are promising (Newman et al., 1993; Kuller et al., 1998), but currently are not widely available, nor have evidence-based guidelines been produced for their use (see Section II.5.c). Thus, selection of older persons for intensive LDL-lowering therapy with drugs requires a considerable degree of clinical judgment and may be less open to a specific guideline. Nonetheless, several factors can be taken into account when selecting older persons for intensive LDL-lowering therapy, particularly for drug therapy.

Framingham risk scoring remains the primary means of identifying older persons at higher risk. Even so, one factor that may add perspective in the selection of older persons for LDL-lowering drugs at different levels of risk projected from risk factors is an estimate of the

number of persons needed to treat (NNT) to achieve benefit. Table II.7–2 gives an estimate of the benefit of statin therapy in older persons over a 15-year period at different levels of projected 10-year risk, assuming that therapy is applied continuously between ages 65 and 80. The assumption is also made that statin therapy reduces risk for all CHD categories by approximately one-third and that for older persons, CHD deaths account for 50 percent of all hard CHD events. No published data provide the ratio of CHD deaths/hard CHD events in older persons, but considering the high mortality in this large group, an estimate of 50 percent appears reasonable.

Table II.7–2. Number Needed to Treat (NNT) with Statin Therapy for 15 Years to Prevent CHD Events by Age 80 Starting at Age 65*

10-Year Risk for Hard CHD†	NNT to Prevent CHD Events (15 Years of Drug Therapy)		
	CHD Death	Hard CHD†	Total CHD‡
10%	42	21	10
20%	20	10	5
30%	13	7	3
40%	10	5	1–2

* The results in this table assume that statin therapy reduces relative risk for all CHD events by one-third (see Table II.2–3).

† Hard CHD includes myocardial infarction + CHD death.

‡ Total CHD includes myocardial infarction, CHD death, unstable angina, and coronary procedures (angioplasty and coronary bypass surgery) (Wilson et al., 1998).

Factors other than the 10-year risk score based on major risk factors may further aid in selection of older persons for intensive LDL-lowering therapy. Since the relative risk accompanying some risk factors declines with advancing age, measures of subclinical atherosclerosis may assist in the identification of older persons who are at high absolute risk and who should benefit from more intensive therapy (see Section II.5.c). For example, a positive ankle-brachial blood pressure index places an older person in a high-risk category (see Section II.5.c.1), as does identification of myocardial ischemia (Section II.5.c.2). The same is true for older persons with advanced subclinical atherosclerosis identified by increased carotid artery thickening or coronary calcium (e.g., $\geq$75th percentile for age or sex) (see Section II.5.c.3). Thus, use of noninvasive measures of myochardial ischemia or subclinical atherosclerosis may be helpful in the selection of older persons who are good candidates for intensive LDL-lowering therapy including drug therapy. Beyond these approaches to risk assessment, however, many other medical and social factors must be taken into account in the selection of older persons for aggressive short-term risk reduction. These are discussed in more detail in Section VIII.3.

j. Selection of persons for long-term primary prevention in the clinical setting

The essential reason for using clinical resources for long-term primary prevention of CHD is to slow the development of coronary atherosclerosis. Long-term prevention in the clinical setting thus represents an extension of the public health approach. Unless coronary atherosclerosis is prevented (or greatly reduced), the total burden of CHD in society will not be substantially

reduced. The lion's share of the effort to prevent coronary atherosclerosis falls to the population (public health) approach; nonetheless, modification of risk factors in persons with a high lifetime risk requires attention by health professionals. A considered judgment is needed for how best to manage such persons. The physician is obliged to identify underlying risk factors (atherogenic diet, overweight/obesity, and physical inactivity) and to introduce risk reduction therapies for them. For the major risk factors, smoking cessation intervention is indicated for cigarette smokers, blood pressure lowering is required for persons with hypertension, and elevated LDL cholesterol should be lowered in those with high levels ($\geq$160 mg/dL) regardless of the presence or absence of other risk factors. Lifestyle intervention is the preferred approach, but in some cases, drug therapy is optional or needed. ATP III outlines approaches to treatment of elevated LDL-cholesterol levels; if clinical management is needed, the report favors therapeutic options that will be robust even for long-term prevention. The absence of other risk factors does not obviate the need to treat elevated LDL cholesterol to reduce build-up of coronary atherosclerosis in the long term.

The concept of long-term prevention highlights the need for early detection of lipid disorders. Early detection links clinical and population approaches to primary prevention at an age when intervention can retard the early stages of atherogenesis. NCEP has long recommended that all adults, starting at age 20, undergo periodic testing for serum cholesterol levels. Some guidelines (Prevention of coronary heart disease in clinical practice 1998; Wood et al., 1998; Joint British recommendations 1998; 2000; Frohlich et al., 1998; Fodor et al., 2000; U.S. Preventive Services Task Force 1996) have recommended that cholesterol testing be delayed until later in life. This recommendation is predicated on the belief that risk can be largely reversed by clinical intervention later in life. A vast body of information on the evolution and natural history of atherosclerosis, however, contradicts this belief. As shown by recent clinical trials with statin therapy, clinical intervention in high-risk populations later in life still leaves many persons with an unacceptably high risk. In other words, if primary atherogenesis is ignored until atherosclerosis has become advanced, intervention to stabilize existing lesions can never reduce risk to the level of a person with minimal coronary lesions. Early detection of cholesterol disorders provides the opportunity to curtail development of coronary atherosclerosis from young adulthood, a time when atherogenesis is beginning to accelerate. Persons at highest long-term risk are those in the upper quartile of cholesterol levels during young adulthood (Anderson et al., 1987; Klag et al., 1993, Stamler et al., 2000). Elevated serum cholesterol belongs among a constellation of risk factors (cigarette smoking, elevated blood pressure, obesity, physical inactivity, and an atherogenic diet) that contributes to build up of coronary atherosclerosis throughout life (Berenson et al., 1992; 1998; Denke et al., 1993; 1994; McGill and McMahan, 1998; Neaton and Wentworth, 1992; Strong et al., 1997; 1999). Early detection of these risk factors, including elevated cholesterol, affords an opportunity to initiate interventions that will arrest or slow the progression of atherogenesis during young adulthood.

An additional important reason to test serum cholesterol in young adults is to identify genetic disorders of lipid and lipoprotein metabolism. Persons with heterozygous familial hypercholesterolemia are at particularly high risk, even in the short term. Although this disorder is not common, it is highly dangerous not only for the affected person, but potentially for first-degree relatives as well. Screening the relatives of persons with heterozygous familial hypercholesterolemia is important in identifying new cases and increasing the number of these

high-risk patients who are subsequently treated with LDL-lowering drug therapy (Umans-Eckenhausen et al., 2001). Moreover, there are other causes of severe hypercholesterolemia (e.g., polygenic hypercholesterolemia) that are more common and also are accompanied by increased risk for premature CHD. These genetic forms of hypercholesterolemia can now be treated effectively, which increases the need for their early detection. For more detail, see Section VII. Management of Specific Dyslipidemias.

The relationship between serum cholesterol levels and lifetime risk for CHD has been evaluated in the Framingham Heart Study. The lifetime risk for total CHD (i.e., all clinical manifestations of CHD) for men and women free of CHD at age 40 years is 1 in 2 for men and 1 in 3 for women; it decreases only slightly with advancing age attained free of CHD (Lloyd-Jones et al., 1999). Even at age 70 the lifetime risk for CHD remains high: 1 in 3 for men and 1 in 4 for women. The lifetime risk for men and women free of CHD at various ages varies according to total cholesterol levels as shown in Table II.7–3 below. Three ranges of total cholesterol are compared: <200, 200–239 mg/dL, and ≥240 mg/dL; these ranges approximately correspond to LDL-cholesterol ranges of <130, 130–159 mg/dL, and ≥160 mg/dL. For men at age 40, the risk of developing CHD in any form over the next 40 years for the three ranges is 31 percent, 43 percent, and 57 percent respectively. Corresponding risks in women are 15 percent, 26 percent, and 33 percent. This is in sharp contrast to the low 10-year risks at age 40. The figures below present the plots of lifetime risk at age 40 (Figure II.7–1) and age 70 (Figure II.7–2) for men (left panel) and women (right panel) at different total cholesterol levels.

These time-dependent risks have implications for ATP III guidelines. Increased lifetime risks associated with high total cholesterol levels (≥240 mg/dL), which correspond to categorically high LDL cholesterol (≥160 mg/dL), are clearly evident and justify clinical therapies to reduce long-term risk. But even borderline-high total cholesterol (200–239 mg/dL) carries significant long-term risk, and it deserves clinical intervention, albeit not necessarily with LDL-lowering drugs.

Table II.7–3. Short-Term and Lifetime Risk of CHD by Cholesterol Levels Obtained at Various Ages (modified from Lloyd-Jones et al., 1999)

	Total Cholesterol Level (mg/dL)					
	<200	200–239	240+	<200	200–239	240+
	Men			Women		
Age 40						
10-year risk	3%	5%	12%	1%	2%	5%
40-year risk	31%	43%	57%	15%	26%	33%
Age 50						
10-year risk	8%	10%	15%	2%	4%	8%
40-year risk	40%	42%	63%	19%	30%	39%
Age 60						
10-year risk	16%	15%	21%	5%	8%	11%
Lifetime risk	34%	41%	51%	20%	24%	36%
Age 70						
10-year risk	18%	22%	28%	5%	7%	13%
Lifetime risk	27%	36%	42%	14%	20%	29%
Age 80						
10-year risk	14%	23%	29%	14%	16%	17%
Lifetime risk	17%	23%	34%	17%	18%	21%

Figure II.7–1. Lifetime Risk of CHD by Total Cholesterol Level for Men (left) and Women (right) at Age 40 Years (derived from Lloyd-Jones et al., 1999)

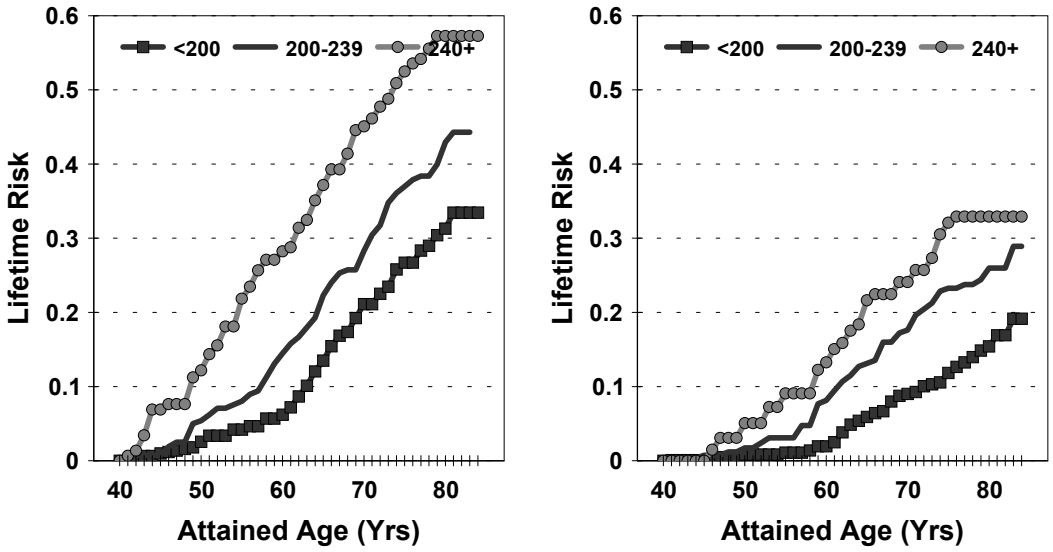
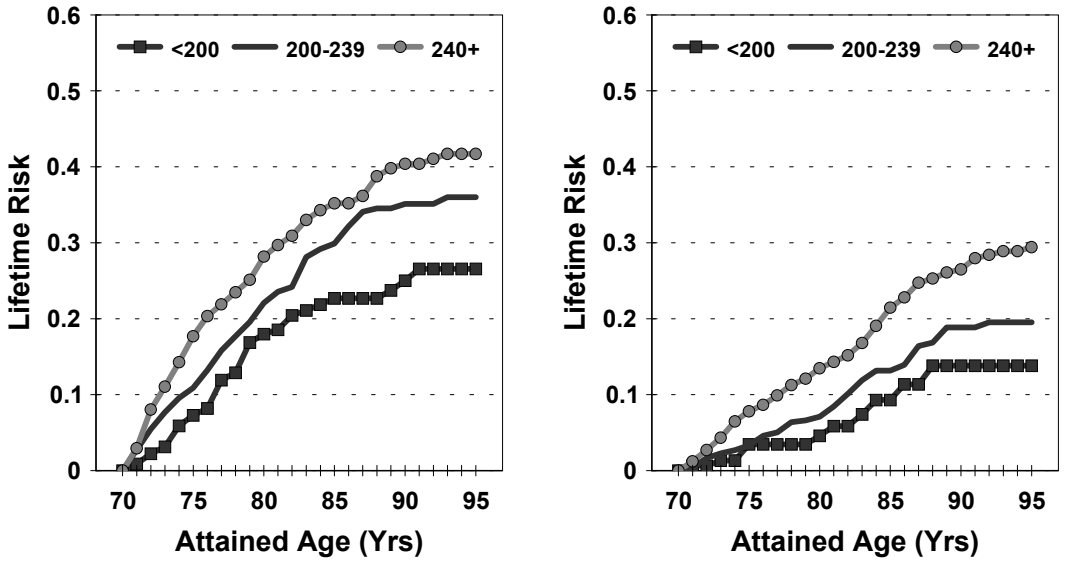


Figure II.7–2. Lifetime Risk of CHD by Total Cholesterol Level for Men (left) and Women (right) at Age 70 Years



The major impediment to long-term primary prevention in clinical practice is the cost of therapy. Costs are incurred in all aspects of clinical intervention, e.g., physician time, dietary therapy, drugs, and monitoring. At present, the cost of drugs appears to predominate. This fact has led some guideline committees in other countries to recommend restricting use of LDL-lowering drugs to persons at high short-term risk (Prevention of coronary heart disease in clinical practice 1998; Wood et al., 1998; Joint British recommendations 1998; 2000; Faergemen 1999). This restriction is considered necessary because of financial constraints that require a conservative allocation of national medical resources. Certainly persons at higher risk in the short term ($\leq$10 years) deserve priority in intervention including use of LDL-lowering drugs. Still, the advantages of preventing coronary atherosclerosis in the first place cannot be ignored. Lifetime prevention of CHD by retarding atherogenesis remains an important goal. Consequently, persons with above-average long-term risk deserve attention by physicians; they are not necessarily candidates for cholesterol-lowering drugs, but at the very least, deserve intervention on life habits. Physicians can use their influence to advocate and support long-term risk reduction.

The issue of long-term prevention with LDL-lowering drugs deserves comment. Elevated LDL cholesterol is the primary driving force for coronary atherogenesis. When LDL-cholesterol levels are high ($\geq$160 mg/dL), atherosclerosis progresses at a relatively high rate. Persons with very high LDL-cholesterol levels ($\geq$190 mg/dL) can develop premature CHD even in the absence of other risk factors. Those with high LDL-cholesterol levels (160–189 mg/dL) can experience premature CHD when other risk factors are present, even when absolute risk at a younger age is <10 percent per 10 years. There is little doubt that LDL-lowering drugs will curtail atherogenesis in these persons. Therefore, use of LDL-lowering drugs in such persons can be justified to achieve the benefits of long-term risk reduction even when drugs are not considered "cost-effective" by conventional analysis. As patents on initial statins expire and competition increases, it is highly likely that costs of LDL-lowering drugs will decline substantially.

Nonetheless, ATP III emphasizes that its goals for LDL cholesterol should be achieved by the most cost-effective means, i.e., by use of maximal dietary therapy before drugs and by choosing the most cost-effective drug regimens. ATP III considers the judicious use of LDL-lowering drugs in long-term prevention to be an "adjunct" to lifestyle changes—and not first-line therapy. For a more detailed discussion of the cost-effectiveness of LDL-lowering therapy, see Section II.14.

k. LDL goals in primary prevention

Prospective epidemiological studies show that the incidence of CHD is proportional to serum total cholesterol and LDL-cholesterol levels. When LDL-cholesterol levels are <100 mg/dL, CHD risk likewise is low, even in the presence of other risk factors (Keys et al., 1980; 1984; Grundy et al., 1990; Wilson et al., 1998). Thus, an LDL cholesterol <100 mg/dL can be called *optimal.* Moreover, when other coronary risk factors are largely absent and LDL-cholesterol concentrations are above but near optimal, i.e., 100–129 mg/dL, the 10-year risk for CHD is relatively low (Stamler et al., 1986; Kannel 1995) (see Table II.7–4).

Table II.7–4. 10-Year Risk for CHD in the Framingham Population for Low Risk and Lowest Risk Persons with LDL Cholesterol Levels 100–129 mg/dL (modified from Wilson et al., 1998)

Age Group (Years)	Average Risk*		Low Risk†		Lowest Risk‡	
	Men	Women	Men	Women	Men	Women
30–39	3%	<1%	1%	0%	0%	0%
40–49	6%	1.5%	2%	1%	1%	0%
50–59	11%	5%	3%	1%	2%	1%
60–69	20%	8%	4%	2%	2%	1%
70–74	25%	11%	6%	3%	3%	1%

* Average 10-year risk for hard CHD (myocardial infarction and CHD death) in the Framingham population regardless of LDL-cholesterol levels.

† Low risk level = 10-year absolute risk for hard CHD (myocardial infarction and CHD death) in a subject with LDL cholesterol 100–129 mg/dL, blood pressure <130/<85 mmHg, no treatment for hypertension, HDL cholesterol 45–59 mg/dL, nondiabetic and nonsmoker.

‡ Lowest risk level = 10-year absolute risk for hard CHD in a subject with LDL cholesterol 100–129 mg/dL, blood pressure <120/<80 mmHg, no treatment for hypertension, HDL cholesterol ≥60 mg/dL, nondiabetic and nonsmoker.

Despite the low risk for CHD accompanying LDL-cholesterol levels that are optimal (<100 mg/dL) or above but near optimal (100–129 mg/dL), the intensity of clinical intervention required to achieve such levels for everyone in the population would financially overload the health care system. Drug usage would rise enormously. Selection of persons for clinical intervention depends on the principle of adjusting intensity of therapy to absolute risk. Persons at higher risk require more intensive therapy to attain the goal of a lower risk LDL level. In ATP III the decision was made to set the primary LDL-cholesterol goals according to the number of major risk factors, as was done in ATP II.

In ATP II (National Cholesterol Education Program 1993; 1994), the LDL-cholesterol goal for persons with multiple (2+) risk factors was <130 mg/dL. This goal is maintained in ATP III. Therapeutic lifestyle changes can be recommended for all such persons whose LDL cholesterol is ≥130 mg/dL at baseline. These changes include an LDL-lowering diet, weight reduction, and increased physical activity. As in ATP II, for persons with multiple risk factors, ATP III continues to recommend consideration of LDL-lowering drugs when LDL-cholesterol levels are ≥160 mg/dL after therapeutic lifestyle changes. However, new evidence outlined in this section supports more intensive therapy to achieve this goal for some persons whose LDL-cholesterol levels are borderline high (130–159 mg/dL) after therapeutic lifestyle changes. Thus, when multiple risk factors are present and 10-year risk for CHD is relatively high (i.e., ≥10 percent), consideration of LDL-lowering drugs is warranted when LDL cholesterol is ≥130 mg/dL after lifestyle changes. Not only is consideration justified by clinical trials that showed that drug therapy is efficacious, but it was found to be cost-effective as well (see Section II. 14. f). Indeed, for those at highest 10-year risk (i.e., >20 percent), an optimal LDL cholesterol is a suitable target goal. On the other hand, when 10-year risk is low to moderate (<10 percent), restricting LDL-lowering drugs to those with LDL cholesterol ≥160 mg/dL still seems appropriate on grounds of both efficacy and cost-effectiveness.

When 0–1 risk factor is present, LDL-lowering therapy need not be as intense because absolute risk is not as high as when multiple risk factors are present. Most persons with 0–1 risk factor have a 10-year risk for CHD <10 percent. In such persons, an LDL-cholesterol goal of <160 mg/dL is allowable. Although a lower level (<130 mg/dL) is nearer to optimal, introduction of drug therapy to treat LDL-cholesterol levels of 130–159 mg/dL when 10-year risk is <10 percent is unrealistic. An enormous number of people would then be drug-eligible. They would require many years of drug therapy before realizing any discernible population benefit; any unrecognized long-term side effects of drugs would be magnified in this large group of lower risk persons; and drug therapy would not be cost-effective by current standards. Whether to consider drug therapy in persons with 0–1 risk factor and LDL cholesterol 160–189 mg/dL after lifestyle changes is more problematic. Their short-term risk is relatively low, and drug therapy is of marginal cost-effectiveness at current drug prices (see Section II.14.f). However, atherogenesis undoubtedly is accelerated, and use of drugs must be deemed optional if other factors (e.g., severe single-risk factors, a family history of premature CHD, life-habit risk factors, or emerging risk factors) are present beyond the count of major risk factors. Finally, when LDL cholesterol is ≥190 mg/dL after lifestyle changes, drug therapy should be considered even in persons with 0–1 risk factor because of accelerated atherogenesis and high long-term risk.

Evidence statements: *A strong relationship exists between LDL-cholesterol levels and CHD risk (C1). An elevated serum total cholesterol contributes to coronary atherosclerosis throughout life; serum total cholesterol levels measured in young adulthood correlate with CHD rates later in life and over a lifetime (C1). For persons without other CHD risk factors, risk for CHD is relatively low when LDL-cholesterol levels are <130 mg/dL (C1). Moreover, for persons with higher LDL-cholesterol levels (≥130 mg/dL), clinical trials document the efficacy of LDL lowering to reduce risk for CHD in primary prevention (A1, B1), particularly when LDL-cholesterol levels are reduced to <130 mg/dL (A1).*

Recommendation: *LDL-lowering therapy should play an important role in primary prevention of CHD in persons at increased risk. For persons at increased risk because of the presence of multiple risk factors, the LDL-cholesterol goal should be <130 mg/dL. Therapeutic lifestyle changes should be initiated in all such persons. Persons with multiple risk factors whose short-term (10-year) risk is low to moderate (<10 percent) generally should not receive LDL-lowering drugs when LDL-cholesterol concentrations are only borderline high (130–159 mg/dL), but drugs should be considered when LDL levels are high (≥160 mg/dL). For higher risk persons with multiple risk factors (10-year risk 10–20 percent), consideration should be given to drug therapy when the LDL goal (<130 mg/dL) cannot be achieved by lifestyle therapies. Finally, multiple-risk-factor persons at highest risk (10-year risk >20 percent) need to attain even lower LDL-cholesterol levels (LDL goal <100 mg/dL), and consideration should be given to starting drug therapy simultaneously with therapeutic lifestyle changes when LDL-cholesterol levels are ≥130 mg/dL.*

Recommendation: *For persons who are otherwise at lower risk (0–1 risk factor), an effort should be made to lower LDL-cholesterol levels to <160 mg/dL. In such persons, lifestyle changes should be emphasized when the LDL-cholesterol level is in the range of 130–159 mg/dL to minimize the risk of any marginal (subcategorical) risk factors. Drug therapy at these LDL levels generally should be avoided, because of lack of long-term data on safety and because of relatively low cost-effectiveness ratios. In persons with 0–1 risk factor, if LDL-cholesterol levels cannot be reduced to <160 mg/dL by therapeutic lifestyle changes, LDL-lowering drugs can be viewed as optional when levels are in the range of 160–189 mg/dL, and should be strongly considered when levels persist at ≥190 mg/dL. Physicans should opt for drug therapy at former levels (160–189 mg/dL) when persons appear to have risk that is greater than that revealed by 0–1 standard risk factor, i.e., because of a severe single-risk factor, a family history of premature CHD, or the presence of life-habit or emerging risk factors.*

Recommendation: *Routine cholesterol testing should begin in young adulthood (≥20 years of age). In young adults, above-optimal LDL-cholesterol levels deserve attention. When LDL-cholesterol concentrations range from 100–129 mg/dL, young adults should be encouraged to modify life habits to minimize long-term risk. In those with borderline high LDL cholesterol (130–159 mg/dL), clinical attention through therapeutic lifestyle changes is needed both to lower LDL cholesterol and to minimize other risk factors. If LDL cholesterol is high (160–189 mg/dL), more intensive clinical intervention should be initiated, with emphasis on therapeutic lifestyle changes. However, if LDL cholesterol remains elevated despite therapeutic lifestyle changes, particularly when LDL cholesterol is ≥190 mg/dL, consideration should be given to long-term management with LDL-lowering drugs.*

8. Secondary prevention: persons with CHD

a. Secondary prevention of recurrent CHD

Persons with established CHD are at very high risk for recurrent CHD. A growing body of evidence indicates that LDL-lowering therapy reduces recurrent coronary events in persons with existing CHD. The results of earlier secondary prevention trials, which were the basis of ATP II

recommendations, are summarized in Table II.8–1. As shown, even before introduction of statins, cholesterol-lowering therapy was found to reduce CHD events without evidence of an increase in noncardiovascular mortality (Rossouw et al., 1990, Rossouw 1994). Subsequent secondary prevention trials with statins documented a reduction in cardiovascular morbidity and mortality and total mortality. These latter trials included those with both angiographic outcomes (Brown et al., 1990; Waters et al., 1994; Pitt et al., 1995; Azen et al., 1996; The Post-CABG Trial Investigators 1997; Holmes et al., 2000) and clinical endpoints (Scandinavian . . . Study Group 1994; Sacks et al., 1996; Long-Term Intervention . . . Study Group 1998). In several of the angiographic trials, a significant decline in the incidence of clinical CHD events was observed in the treated group in a period of only two years (Table II.2–2). This finding makes it probable that the instability of plaques (which leads to fissuring, thrombosis, and intramural hemorrhage) is reduced as well (Constantinides 1990; Brown et al., 1993; Falk et al., 1995; Levine et al., 1995; Ballantyne 1998). The three major secondary prevention trials with statins were the Scandinavian Simvastatin Survival Study (4S) (Scandinavian . . . Study Group 1994), Cholesterol and Recurrent Events (CARE) Study (Sacks et al., 1996), and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study (Long-Term Intervention . . . Study Group 1998). Results of these trials are summarized in Table II.8–2. All three showed reductions in recurrent myocardial infarction and coronary death, coronary artery procedures, and stroke. Two of the trials reported a reduction in total mortality with statin therapy. Thus, secondary prevention trials provide strong evidence for the benefit of cholesterol-lowering therapy in persons with established CHD.

Table II.8–1. Earlier Secondary Prevention Trials: Morbidity and Mortality Results*†

Event	Proportion of Deaths	Relative Risk	Confidence Interval
Nonfatal myocardial infarction	—	0.74	0.66–0.84
Fatal myocardial infarction	73%	0.86	0.77–0.96
Cardiovascular deaths	90%	0.89	0.79–1.00
Cancer deaths	5%	0.89	0.59–1.39
Other deaths	4%	1.14	0.71–1.82
All deaths	100%	0.91	0.81–1.01

* Meta-analysis by Rossouw based on Rossouw et al., 1990; Rossouw 1991.

† Trials include Medical Research Council's low-fat diet trial (Research Committee 1965), Medical Research Council's soya-bean oil trial (Research Committee . . . 1968), Scottish Society of Physician's clofibrate trial (Research Committee . . . 1971), Stockholm Ischaemic Heart Disease Secondary Prevention Study (Carlson and Rosenhamer, 1988), Coronary Drug Project's clofibrate trial (Canner et al., 1986; Coronary Drug Project . . . 1975), Coronary Drug Project's niacin trial (Canner et al., 1986; Coronary Drug Project . . . 1975), and Program on the Surgical Control of Hyperlipidemias (Buchwald et al., 1990).

Table II.8–2. Major Secondary Prevention Trials with Statins: Morbidity and Mortality Results

Study	Persons	Duration	Drug (dose/d)	Baseline LDL-C (mg/dL)	LDL-C Change	Major Coronary Events	Revascu-larization	Coronary Mortality	Total Mortality	Stroke
4S	4444	5.4 yrs	Simvastatin 10/40 mg	188	-35%*	-35%*	-37%*	-42%*	-30%*	-27%*
CARE	4159	5 yrs	Pravastatin 40 mg	139	-27%*	-25%*	-27%*	-24%*	-9%	-31%*
LIPID	9014	5 yrs	Pravastatin 40 mg	150	-25%*	-29%*	-24%*	-24%*	-23%*	-19%*

* Statistically significant changes at $p<0.05$ or lower.

Recent statin trials also reveal the impact of LDL lowering on selected populations and on additional clinical endpoints. LDL lowering has been shown to produce marked benefit regardless of gender, age, and the presence of diabetes, smoking, and hypertension (Byington et al., 1995; Sacks et al., 1996; Waters et al., 1995; Kjekshus et al., 1995; Pyörälä et al., 1997; Miettinen et al., 1997; Goldberg et al., 1998). Furthermore, in CHD patients, LDL lowering decreases stroke rates (Scandinavian . . . Study Group 1994; Sacks et al., 1996; Crouse et al., 1997; Hebert et al., 1997; Long Term Intervention . . . Study Group 1998), improves angina and myocardial perfusion (Anderson et al., 1995; Kjekshus and Pedersen, 1995; Aengevaeren et al., 1997; Pedersen et al., 1998a; Gould et al., 1998), and decreases the need for subsequent revascularization (Scandinavian Simvastatin Survival Study Group 1994; Sacks et al., 1996; The Post-CABG Trial Investigators 1997; LIPID Study Group 1998; Knatterud et al., 2000).

ATP II (National Cholesterol Education Program 1993, 1994) identified the LDL-cholesterol goal for secondary prevention to be a level $\leq$100 mg/dL. Recent clinical trials provide an opportunity for reexamination of this goal. Epidemiological data strongly suggest that the prevalence of CHD is lowest when the LDL-cholesterol level is <100 mg/dL. Large studies and meta analyses have revealed that CHD rates decrease with declining cholesterol levels down to a total cholesterol of 150 mg/dL, corresponding to an LDL cholesterol of about 100 mg/dL (Stamler et al., 1986; Law et al., 1994b; Law 1999; Holme 1996). Epidemiological data demonstrate a continuous (log-linear) relationship between LDL cholesterol (and total cholesterol) and CHD risk (Law et al., 1994b; Law 1999). The log-linear relationship holds to levels of LDL cholesterol below 100 mg/dL (Chen et al., 1991). Factors that increase risk (e.g., presence of CHD) shift the curvilinear relationship, increasing the risk impact of LDL cholesterol at lower ranges (Cullen et al., 1997). Models based upon epidemiological data support the concept that LDL-lowering treatment at baseline total cholesterol levels >200 mg/dL (comparable to baseline LDL of approximately 130 mg/dL) will lower mortality and morbidity (Grover et al., 1992). Finally, Law et al. (Law et al., 1994b; Law 1999) reported that results of epidemiological studies and clinical trials are highly congruent, providing additional support for the applicability of epidemiological data for setting LDL-cholesterol goals in secondary prevention.

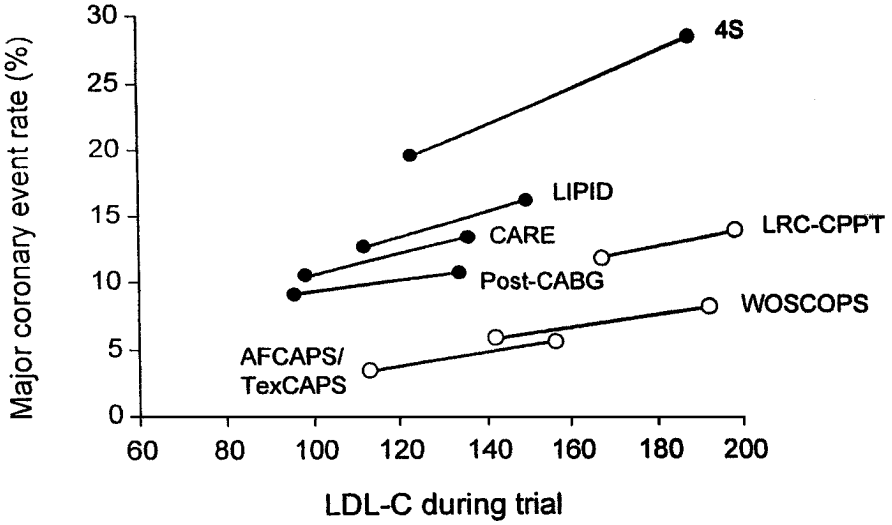
Angiographic studies on the whole are consistent with maximal CHD reduction in secondary prevention occurring at LDL levels <100 mg/dL. Three studies are particularly noteworthy:

POSCH (Buchwald et al., 1990; 2000), FATS (Brown et al., 1990), and Post-CABG (The Post-CABG Trial Investigators 1997). POSCH (using surgery) and FATS (using nicotinic acid and a statin or sequestrant) achieved LDL levels near 100 mg/dL and showed favorable changes in coronary lesions. The Post-CABG trial tested the concept that a lower LDL is better by examining the benefits of moderate versus aggressive LDL lowering on progression of atherosclerosis in saphenous vein grafts. Using a statin and sequestrant if needed, the moderate treatment group was treated to maintain LDL levels between 130–140 mg/dL, and the aggressive treatment group was titrated to a target LDL of <95 mg/dL. The aggressively treated group had less progression, fewer new lesions, and needed less revascularization (The Post-CABG Trial Investigators 1997; Knatterud et al., 2000).

Post-hoc analyses of statin trials clearly show benefit from LDL cholesterol lowering to the range of 100 to 125 mg/dL (Grundy 1998b; Sacks et al., 1998; Pedersen et al., 1998b; Gotto et al., 1999). Not all of the studies confirm that an optimal LDL cholesterol is <100 mg/dL; however, in subgroup analysis the statistical power to reliably define the lower limit of benefit may be lacking. In the 4S trial (Pedersen et al., 1998b), lowering of LDL levels gave proportional and continuous but progressively smaller absolute decrements in CHD risk down to an LDL cholesterol of 100 mg/dL. In CARE (Sacks et al., 1996; 1998) benefit with statin treatment was seen with mean on-therapy LDL-cholesterol levels in the range of 100 mg/dL throughout the study (Figure II.8–1). Although CARE and LIPID could not rule out a threshold relation at LDL cholesterol less than 125 mg/dL, the combined data from epidemiological, angiographic (Blankenhorn et al., 1993; Brown et al., 1997; Brown and Zhao, 2000; Kroon et al., 1996), and other clinical trials support an LDL-cholesterol goal of <100 mg/dL for secondary prevention.

Recently, clinical trials have examined the effect of treatment to lower LDL cholesterol goals, and earlier treatment of patients. Although no single trial conclusively confirms a specific LDL-cholesterol goal lower than 100 mg/dL, six studies showed a clinical benefit in the treatment group with on-treatment LDL cholesterol from 72 mg/dL to 98 mg/dL (Schwartz et al., 2001 [MIRACL]; Pitt et al., 1999 [AVERT]; Blankenhorn et al., 1993 [MARS]; Kroon et al., 1996 [LAARS]; Post-CABG, Brown et al., 1997 [FATS extension]; Brown BG et al., 2000 [HATS]). The totality of this data suggests that further benefit accrues in patients treated to an LDL-cholesterol level below 100 mg/dL. It is not known whether LDL levels markedly below 100 mg/dL versus marginally below 100 mg/dL confer any additional benefit. Trials with clinical endpoints (AVERT, MIRACL) and other endpoints, including vascular function, confirm an early (1 week to 3 months) benefit of statin treatment for patients with atherosclerosis or acute coronary syndromes. In this regard MIRACL is noteworthy, demonstrating that statin treatment initiated in hospital (in patients with non-Q MI or unstable angina) was safe and was associated with a 16 percent relative risk reduction at 16 weeks. Also supporting the concept of early treatment is a recently published, very large observational study from Sweden. In-hospital initiation of statin treatment was associated with an adjusted 25 percent lowering of total mortality at 1 year (Stenestrand and Wallentin, 2001).

Figure II.8–1. Relation of CHD Events to LDL Levels in Treatment and Placebo Groups: Statin Trials



(Waters and Azar, 2000)

The recent VA-HIT trial (Rubins et al., 1999), however, revealed that modification of other lipid risk factors could reduce risk for CHD when LDL cholesterol is in the range of 100 to 129 mg/dL (Tables II.8–3a–b). In this trial, persons with low LDL (mean 112 mg/dL) were treated with gemfibrozil for 5 years. Gemfibrozil therapy, which raised HDL and lowered triglyceride, reduced the primary endpoint of fatal and non-fatal myocardial infarction by 22 percent without significantly lowering LDL-cholesterol levels. This study thus raises the possibility of efficacy from optional use of non-statin drugs when LDL-cholesterol levels in CHD patients are in the range of 100–129 mg/dL.

Table II.8–3a. Veterans Affairs HDL Intervention Trial (VA-HIT): Lipids and Lipoproteins

Persons	Drug/Duration	Total Cholesterol (mg/dL)	LDL Cholesterol (mg/dL)	HDL Cholesterol (mg/dL)	Trigly-ceride (mg/dL)	Non-HDL cholesterol (mg/dL)
2531 men	Gemfibrozil (1200 mg/day) 5.1 years	175*	111*	32*	161*	143*
	% Difference (Treatment minus Control)	-4%	0%	+6%	-31%	-6%

* Baseline levels.

Table II.8–3b. Veterans Affairs HDL Intervention Trial (VA-HIT): Cardiovascular Events: Percent Risk Reduction (95 percent Confidence Intervals)

Non-Fatal Myocardial Infarction + CHD Death	CHD Death	Non-Fatal Myocardial Infarction	Stroke	Revascularization	Total Mortality
22%*	22%	23%†	31%‡	9%	11%
(7 to 35%)	(-2 to 41%)	(4 to 38%)	(2 to 52%)	(-8 to 23%)	(-8 to 27%)

* Primary endpoint, p = 0.006.

†, ‡ secondary endpoints, p = 0.02 and 0.036, respectively.

Despite the strongly positive result of gemfibrozil therapy in the VA-HIT trial, less striking results have been reported for other fibrate trials in secondary prevention. For example, the clofibrate arm of the early Coronary Drug Project (Coronary Drug Project Research Group 1975) produced no evidence of benefit. Another early secondary prevention trial (Research Committee 1971) with clofibrate gave more favorable outcomes, but the reduction in CHD events was not statistically significant. Results from the recent BIP trial with bezafibrate therapy were essentially negative (Bezafibrate Infarction Prevention Study 2000). This secondary prevention study recruited patients with a mean LDL cholesterol >130 mg/dL; in similar CHD patients, both CARE and LIPID trial results were strongly positive with statin therapy. Thus, statin therapy is clearly preferred over fibrates in patients with borderline high or high LDL cholesterol (≥130 mg/dL). Nonetheless, VA-HIT findings support the potential for significant additional risk reduction in patients with low LDL cholesterol (<130 mg/dL). VA-HIT results also support a positive trend for CHD events (although not for all-cause mortality) when all fibrate trials are considered together (Gordon 2000).

***Evidence statements**: Secondary prevention trials demonstrate that reduction of LDL-cholesterol levels significantly reduces risk for recurrent major coronary events in persons with established CHD (A1). Evidence from end-point trials with cholesterol-lowering drugs, angiographic trials, and epidemiological studies indicates that maximal CHD reduction occurs when LDL cholesterol is <100 mg/dL (A2, B1, C1).*

***Recommendation**: Persons with established CHD should receive intensive LDL-lowering therapy. The goal of therapy in persons with established CHD should be LDL cholesterol <100 mg/dL.*

***Evidence statement**: Persons with established CHD who have a baseline LDL cholesterol ≥130 mg/dL receive benefit from institution of LDL-cholesterol-lowering drugs (A1).*

***Recommendation**: Persons with established CHD who have a baseline LDL cholesterol ≥130 mg/dL should be started on a cholesterol-lowering drug simultaneously with therapeutic lifestyle changes and control of nonlipid risk factors (therapeutic lifestyle changes alone are unlikely to achieve the LDL-cholesterol goal of <100 mg/dL).*

***Evidence statements**: Persons with established CHD who have a baseline LDL cholesterol of 100–129 mg/dL likely will benefit from reducing LDL cholesterol to <100 mg/dL (A2, B2, C1). These persons also appear to benefit from therapy that modifies atherogenic dyslipidemia (A2, B2).*

***Recommendation**: Several options should be considered for treatment of CHD patients with baseline LDL-cholesterol levels of 100–129 mg/dL. These include use of a cholesterol-lowering drug, maximization of therapeutic lifestyle changes, use of a drug to modify atherogenic dyslipidemia, and intensified control of nonlipid risk factors.*

b. Effects of lipid-lowering therapy on stroke

Recent clinical trials in patients with established CHD indicate that lipid-lowering therapy, especially with statins, reduces risk for stroke. A significant reduction in stroke was reported in all three major clinical trials with statins—4S (Pedersen et al., 1998a), CARE (Plehn et al., 1999), and LIPID (Long-Term Intervention . . . Study Group 1998; White et al., 2000). A similar result was obtained with a meta-analysis of several smaller clinical trials with pravastatin (Byington et al., 1995). Subsequent meta-analysis of all statin trials revealed that statin therapy reduces stroke in patients with established CHD by 27–31 percent (Blauw et al., 1997; Hebert et al., 1997; Crouse et al., 1998). Subsequent analyses of pooled pravastatin studies confirm benefit of statin therapy on strokes (Byington et al., 2001). The mechanisms whereby statin therapy reduces stroke in CHD patients are not well understood but probably involve retardation of plaque progression, plaque stabilization, and reduction of the risk for coronary events (Crouse 1999). Regardless, reduction in stroke is definitely an added benefit of statin therapy in secondary prevention. Besides statin therapy, treatment with gemfibrozil in patients with established CHD in the VA-HIT trial reduced investigator-designated stroke by 25 percent, confirmed stroke by 25 percent, and transient ischemic attacks by 59 percent (Rubins et al., 1999). In summary, lipid lowering, particularly with statins, reduces risk for stroke in patients with established CHD. The question of whether LDL-lowering therapy in primary prevention also reduces stroke has not been adequately tested, although one meta-analysis (Hebert et al., 1997) showed a strong trend towards benefit.

***Evidence statement:** In persons with established CHD, LDL-lowering therapy reduces risk for stroke (A1, B1).*

***Recommendation:** For persons with established CHD, LDL-lowering therapy should be carried out to reduce the risk for stroke and for recurrent coronary events.*

9. Total mortality considerations and therapeutic safety

Beyond the striking reduction in CHD rates accompanying lowering of LDL cholesterol lies the question of whether cholesterol-lowering therapy will actually extend the life span. At the time of publication of ATP II (1993), the net impact of cholesterol lowering on mortality was an area of controversy. Previous clinical trials generally had not been designed with sufficient power to

address all-cause mortality. In the early 1990s, several meta-analyses found that mortality from all causes was essentially identical in treated and control persons, despite a significant reduction in CHD mortality (Holme 1990; Muldoon et al., 1990; Rossouw et al., 1990; Ravnskov 1992; Smith et al., 1993; Holme 1993; Gould et al., 1995). This finding raised concerns that cholesterol lowering per se might be causing an increase in non-CHD mortality that offset the reduction in CHD. This concern was reinforced by reports that total mortality rates in populations are relatively high in subgroups with the lowest cholesterol levels.

Further analysis of earlier trials yielded possible explanations for a failure of reduced CHD event rates to translate into reduced mortality rates (Gordon 2000). For example, drugs such as estrogen, dextrothyroxine, and possibly clofibrate, may have had toxicity that obscured the benefit of other drugs. Also, a reduction in all-cause mortality is difficult to detect when total deaths from CHD in clinical trials are relatively low. For instance, all-cause mortality was reduced in secondary prevention trials (where 80 percent of deaths were due to CHD) but were increased in primary prevention trials that included potentially toxic drugs (where only 37 percent of deaths were due to CHD). Finally, the modest degree of cholesterol lowering in most of the earlier trials probably was insufficient to test the hypothesis that treatment reduced total mortality. Analyses of the earlier trials indicated that the crossover point where the reduction in CHD mortality began to outstrip the increase in non-CHD mortality was at an 8–10 percent reduction in serum cholesterol (Holme 1996; Gould et al., 1998).

Since the ATP II report, trials using statins have been reassuring for total mortality considerations. Five large long-term cholesterol-lowering trials using statins, as well as 11 smaller trials of 2–4 years duration, were published between 1993 and 1999 (Furberg et al., 1994; Scandinavian . . . Study Group 1994; MAAS Investigators 1994; Shepherd et al., 1995; Salonen et al., 1995; Pitt et al., 1995; Crouse et al., 1995; Sacks et al., 1996; Mercuri et al., 1996; Post Coronary Artery Bypass Graft Trial Investigators 1997; Downs et al., 1998; Long-Term Intervention . . . [LIPID] Study Group 1998). In these trials, which encompass more than 17,000 statin treated persons followed for an average of 5 years, statin drugs have consistently produced reductions of 18 percent or more in serum cholesterol levels, and have been remarkably free of adverse effects. Two of the large secondary prevention trials, 4S (Scandinavian . . . Study Group 1994) and LIPID (Long-Term Intervention . . . Study Group 1998), demonstrated significant reductions in mortality by themselves, and several others showed clear trends in the same direction. Meta-analysis of these trials shows an overall 29 percent reduction in CHD mortality ($P < 0.001$) and an 11 percent reduction in non-CHD mortality ($P = 0.06$). All-cause mortality was reduced by 22 percent ($P < 0.001$). Finally, a global meta-analysis incorporating 40 trials using statins, fibrates, sequestrants (or partial ileal bypass surgery), nicotinic acid, and/or diet to lower cholesterol now shows a 12 percent reduction in all-cause mortality ($P < 0.001$) (Table II.9–1). The results in Table II.9–1 constitute a refinement of a recent meta-analysis reported by Gordon (2000). Results were prepared for ATP III by panel members D. Gordon and M.A. Proschan.

Table II.9–1. Meta-Analysis of Mortality in Cholesterol-Lowering Trials by Treatment Modality

Treatment Modality	Number of Trials	Number (Treatment/ Control)	% Δ Cholesterol	Mortality	
				Deaths	OR (P)
Statins	17	18494/18449	20%	1107/1381	.78 (<.001)
Fibrates	7	10654/12999	9%	859/1277	1.03 (.58)
			CHD Mortality for Fibrates →	495/884	.93 (.24)
			Non-CHD Mortality for Fibrates →	364/393	1.19 (.02)
Sequestrants	5	3562/3530	12%	159/191	.81 (.06)
Other*	14	4025/5801	10%	789/1293	.93 (.19)
All trials†	42	36775/37321	15%	2914/3420	.88 (<.001)

* Nicotinic acid, diet, and various combinations of drugs.

† Multi-armed trials (CDP, STARS) are counted only once in the totals although their arms can contribute to more than one row.

Evidence statements: *Overall Benefit of Cholesterol Lowering on Mortality. LDL-lowering therapy reduces total mortality, i.e., extends life, by decreasing CHD mortality (A1, B1). This therapeutic benefit was unclear in earlier trials using interventions with limited cholesterol lowering (10 percent), some of which showed adverse non-CHD effects. However, in trials using statins, in which cholesterol levels were reduced by 20 percent and non-CHD mortality was not increased, the reduction in mortality is incontrovertible.*

Evidence statements: *Benefit of Cholesterol Lowering on Mortality in Secondary Prevention. The benefits of cholesterol lowering on longevity are particularly clear in CHD patients and other high-risk populations due to their high short-term mortality rates when left untreated and to the high proportion of those deaths caused by CHD (A1, B1). In persons with established CHD, a reduction in CHD deaths by effective cholesterol-lowering therapy more than outweighs any side effects of drug therapy.*

Evidence statements: *Benefit of Cholesterol Lowering on Mortality in Primary Prevention. Primary prevention trials using statins show a significant reduction in CHD mortality, no increase in non-CHD mortality, and a strong trend towards lower overall mortality (A2). Because of the lower proportion of deaths that are due to CHD in primary prevention trials (relative to secondary prevention), the latter trend is not significant. The statin trials lasted an average of five years; longer-term observational studies offer a better indication of the potential lifelong impact of cholesterol reduction on mortality (C1). The lack of overall reduction in mortality in primary prevention trials performed before the advent of the statins can be explained by their modest cholesterol reduction (<10 percent) and in some instances by adverse non-CHD effects not seen with the statins.*

Beyond the recent clinical trials showing a reduction in total mortality from LDL-lowering therapy, questions remain about short-term and long-term safety of specific LDL-lowering modalities. The dispute about the safety of lowering of LDL per se has been resolved, at least for

the short term; net benefits in high-risk persons exceed any adverse effects. Furthermore, no evidence for adverse effects of dietary therapy has been uncovered for the short term; in contrast, the optimal diet for long-term prevention of CHD remains an issue under investigation (see Section V). The fact that all drugs potentially carry side effects must be kept in mind when using them for prevention of CHD. Consideration can first be given to short-term side effects. Bile acid sequestrants cause a variety of gastrointestinal side effects, although none of these is apparently life threatening (Lipid Research Clinics Program 1984a,b). Nicotinic acid has numerous short-term side effects, and some persons can develop severe liver toxicity (Coronary Drug Project Research Group 1975). Overall, however, clinical experience does not suggest an increase in non-CHD mortality from use of nicotinic acid. Statins have proven to be remarkably free of short-term side effects, although occasionally persons develop severe myopathy. Controversy persists about the short-term safety of fibrates. Therapy with these drugs can cause myopathy and gallstones. Moreover, in the WHO clofibrate trial (Committee of Principal Investigators 1978), the treatment group showed an increase in total mortality, compared to the placebo group. The reasons for the higher mortality were never identified. Otherwise, a statistically significant higher mortality from non-CHD causes has never been observed in other clinical trials using fibrate therapy. Nonetheless, when all fibrate trials are combined in meta-analysis, the results of the large WHO trial overshadow other trials and lead to a persistent increase in non-CHD mortality. Many investigators, however, doubt that fibrate therapy carries an increased risk for fatal side effects in the short term. But the results of the WHO trial remain a reminder that fibrates should be limited to persons in whom they will provide the greatest benefit, such as those with hypertriglyceridemia (Huttunen et al., 1991) or the metabolic syndrome (Rubins et al., 1999).

The issue of long-term safety of LDL-lowering drugs cannot be resolved by short-term clinical trials. There is always the possibility that chronic administration of drugs will lead to unanticipated side effects. There is no evidence that currently used cholesterol-lowering drugs promote development of cancer or induce subtle neurological diseases. Moreover, clinical experience with these drugs over periods of 30 years for fibrates and bile acid sequestrants and 15 years for statins has uncovered no long-term side effects. Nonetheless, the possibility of long-term side effects, albeit remote, should be one factor to consider when recommending lifetime therapy with a cholesterol-lowering drug.

10. Magnitude of reduction in CHD risk

Clinical trials (Downs et al., 1998; Pedersen et al., 1998b; Long-Term Intervention. . . Study Group 1998; Lipid Research Clinics Program 1984b; Sacks et al., 1996; Scandinavian . . . Study Group 1994; Shepherd et al., 1995) provide the best estimate of the actual reduction in CHD risk that can be achieved by treating high blood cholesterol. However, the trials reflect the impact of short-term cholesterol lowering only; more benefit should accrue with longer treatment. In most trials, treatment duration was 5 years and the average time to event was 2–3 years (assuming that about half the events occur after the midpoint of the trial). Despite the relatively short exposure to treatment, regression analyses relating the percent cholesterol reduction to risk of CHD predict that for every 10 percent reduction in serum cholesterol, there will be a 15 percent reduction in CHD events (Gould et al., 1998). In the major statin trials the absolute reduction in serum cholesterol (and LDL cholesterol) averaged 45 mg/dL. This corresponds to a 20 percent lowering

in serum cholesterol and resulted in a 30 percent reduction in CHD risk (LaRosa et al., 1999; Gordon 2000). The average reduction in LDL cholesterol was 28 percent; thus in the short term CHD risk will be reduced by 10 percent for every 10 percent that LDL cholesterol is lowered. This relationship holds true for primary and secondary prevention, largely unrelated to baseline levels of serum cholesterol in the trials.

It is conceivable that a longer duration of treatment will result in a further reduction in CHD risk. Ecologic studies (i.e., international comparisons) (Stamler et al., 1986; Law et al., 1994b; Law 1999) suggest that differences in levels of serum cholesterol explain almost all of the differences in CHD rates between populations, and a lifelong exposure to a lower average cholesterol level has a marked effect on lowering CHD risk. Regression equations indicate that a difference in total cholesterol level of 23 mg/dL, or approximately 10 percent for a typical Western population, is accompanied by a 30 percent difference in CHD rates (Law et al., 1994a,b; Law 1999). Cohort studies relating individual serum cholesterol levels to future risk over several decades indicate that a 23 mg/dL (10 percent) decrease in serum cholesterol is associated with a 25 percent reduction in CHD risk (Law 1994b; Law and Wald, 1994; Law 1999). Thus, both ecologic studies and cohort studies suggest a more powerful long-term effect on CHD risk than that found in clinical trials. For a 10 percent reduction in serum cholesterol, the ecologic studies suggest a 30 percent reduction in CHD risk, the cohort studies a 25 percent reduction, and the clinical trials actually found 15 percent. The main reason for this difference is likely to be the duration of exposure to a given cholesterol level. In addition, other favorable lifestyle attributes (especially related to diet and physical activity) that are associated with lower cholesterol levels can reduce risk.

Evidence statements: *In short term, controlled clinical trials, a 1 percent reduction in LDL-cholesterol levels on average reduces risk for hard CHD events (myocardial infarction and CHD death) by approximately 1 percent (A1). Cohort studies suggest that a more prolonged reduction in LDL-cholesterol levels will produce an even greater reduction in CHD risk (C1). In the absence of long-term clinical trials, maximal long-term risk reduction cannot be estimated with certainty.*

11. CHD as a risk indicator

The older literature suggested that having coronary disease increased future CHD event risk approximately 7 fold compared to healthy individuals, with an absolute risk of 50–60 percent per decade (Rossouw et al., 1990; Rossouw 1991). CHD rates and case-fatality rates in the United States and in most other developed countries have fallen considerably over the last two decades (Tunstall-Pedoe et al., 1999; Rosamond et al., 1998). Extrapolating from the in-trial experience, the placebo groups in two recent secondary prevention trials (CARE, LIPID) of persons with "average" cholesterol levels had absolute risks for CHD of about 26 percent per decade (Sacks 1996; Long-Term Intervention . . . Study Group 1998). In 4S, the placebo group had high cholesterol levels and an absolute risk of about 56 percent per decade, while in the VA-HIT population with low HDL-cholesterol levels it was about 43 percent per decade (Scandinavian . . . Study Group 1994; Rubins et al., 1999). In women with existing CHD, rates were similar to men, and older persons had higher rates than younger persons (LaRosa et al.,

1999; Hulley et al., 1998). Given that clinical trial participants are likely to have event rates lower than that of similar persons in the general population (due to the healthy volunteer effect), and that the event rates likely will increase as the participants age beyond the typical 5–6 year trial periods, an event rate of 20 percent per decade in persons with CHD represents a minimum estimate of the absolute annual risk associated with existing CHD. A subgroup of the WOSCOPS men with prior evidence of vascular disease (angina, claudication, stroke, TIA, or ECG abnormalities) had an annual rate of CHD of approximately 26 percent per decade, similar to that observed in the secondary prevention trials of persons with prior myocardial infarction or unstable angina (Shepherd et al., 1995). Persons with stable angina pectoris and persons who have had coronary revascularization procedures also have a 20 percent risk of CHD events over 10 years (Knatterud et al., 2000; Feit et al., 2000; Peduzzi et al., 1998). Thus, it appears that evidence of coronary disease short of clinical MI carries the same future risk for CHD as does MI. In most studies, the minimal rate of recurrent, major coronary events in persons with any clinical evidence of CHD appears to be >20 percent over 10 years.

Evidence statement: *Persons with established CHD in the United States have a risk for recurrent myocardial infarction and CHD death (hard CHD) that exceeds 20 percent per 10 years (C1).*

12. Concept of CHD risk equivalents

Some persons without established CHD will have an absolute, 10-year risk for developing major coronary events (myocardial infarction and coronary death) equal to that of persons with CHD, i.e., >20 percent per 10 years. Such persons can be said to have a *CHD risk equivalent.* These persons belong in a high-risk category for primary prevention. Three groups of persons with CHD risk equivalents are identified.

a. Other forms of clinical atherosclerotic disease

Atherosclerosis is a generalized macrovascular disease. Population-based autopsy studies have demonstrated that atherosclerotic disease in one region of the arterial tree is associated with and predicts disease in other arterial regions. The pathobiology and predisposing risk factors are similar for atherosclerosis in coronary, peripheral, and carotid arteries. Further, there is growing evidence that clinical atherosclerotic disease in non-coronary arteries is a powerful predictor of CHD. However, the conclusion that non-coronary forms of atherosclerosis represent a CHD risk equivalent must be derived from the totality of prospective studies because few if any studies were designed specifically to test this hypothesis. The available data relating non-coronary forms of atherosclerosis to CHD are reviewed in the following discussion.

1) Peripheral arterial disease (PAD)

In Table II.12–1, crude rates of CHD are shown for five studies of persons with atherosclerotic peripheral arterial disease (PAD). The Edinburgh Artery Study (Leng et al., 1996) included 1,592 middle-aged men and women. One third of the persons had established CHD. PAD was diagnosed by the ankle/brachial blood pressure index (ABI). Those with a categorical

abnormality (ABI <0.9) had an annual event rate for major coronary events of 2.4–3.8 percent per year. In the Multicenter Study of Osteoporotic Fractures (Vogt et al., 1993), ABI was measured in 1,027 women without CHD. Those with ABI <0.9 had an annual rate for *total CHD mortality* of 2.9 percent per year. The outcome was similar to that for 495 women with pre-existing CHD. In the San Diego cohort of the Lipid Research Clinic study (Criqui et al., 1985; 1992), persons with documented PAD (without CHD) had a *total CHD mortality* of 2 percent per year. In another cohort of persons of whom 40 percent had co-existing CHD, McKenna et al. (1991) reported a very high CHD mortality for persons with categorically low ABI ($\leq$0.85). A similarly high mortality also was reported by Poulias et al. (1992) in 1,000 persons undergoing aortofemoral bypass. These studies taken together support the concept that PAD, whether diagnosed by ABI, lower limb blood flow studies, or clinical symptoms, is a CHD risk equivalent.

Table II.12–1. Crude CHD Event Rate in Persons with Atherosclerotic Peripheral Artery Disease by Study

Study and Design	Number of Subjects; Ages	Subsequent CHD mortality or event rate
Edinburgh Artery Study (Leng et al., 1996) Ankle/brachial blood pressure index (ABI) in randomly selected population 5 year follow-up	1592 men and women 614 had CHD Ages: 55–74	During follow-up, 137 fatal and nonfatal CHD events occurred. CHD event outcomes per year were: 1.4% in those with ABI >1.1 1.4% in those with ABI 1.1–1.01 1.8% in those with ABI 1.0–0.91 2.4% in those with ABI 0.9–0.71 3.8% in those with ABI <0.7
Multicenter Study of Osteoporotic Fracture (Vogt et al., 1993) ABI testing 4.3 yr follow-up	1027 women without CHD; 495 women with CHD Ages: 65–93	During follow-up, 15 CHD deaths occurred in women without CHD. CHD mortality outcomes per year were: 0.2% for women with normal ABI (>0.9) 2.9% for women with ABI <0.9 During follow-up, 17 CHD deaths occurred in women with CHD. CHD mortality outcomes per year were: 0.7% for women with ABI >0.9 3.0% for women with ABI <0.9
LRC San Diego cohort (Criqui et al., 1985 ; 1992) Noninvasive testing lower limb blood flow 4 yr follow-up (Criqui et al., 1985) 10 yr follow-up (Criqui et al., 1992)	257 men 310 women 31 men and 28 women had CHD Ages: 38–82	During 4 yr follow-up of entire cohort, 17 died of CHD. CHD mortality outcomes per year were: 159 subjects had peripheral vascular disease 2% CHD mortality 408 subjects had normal noninvasive testing 0.1% CHD mortality During 10 yr follow-up of those without baseline CHD, 12 men and 6 women died of CHD. CHD mortality outcomes per year were: 0.4% in men without vascular disease 2.5% in men with peripheral vascular disease 0.2% in women without vascular disease 0.4% in women with peripheral vascular disease
McKenna et al., 1991 Persons underwent ABI for evaluation of peripheral artery disease Average 3 yr follow-up (2–10yr)	744 men and women Ages: 19–89	During follow-up, 101 CHD deaths occurred. CHD mortality outcomes per year were: 2% in persons with ABI >0.85 6% in persons with ABI 0.85 40% of persons with ABI 0.85 had history of CHD; 29% persons with ABI >0.85 had history of CHD.
Poulias et al., 1992 Persons undergoing aortofemoral bypass Follow-up: 1 mo to 20 yr (average 8 yr)	941 men and 59 women Ages: 35–87	During followup, 192 CHD deaths occurred CHD mortality outcome: 2.4%/yr

2) Carotid artery disease

The association between symptomatic carotid disease and future coronary morbidity and mortality derived from sizable reported studies is shown in Table II.12–2a. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (Ferguson et al., 1999), symptomatic patients undergoing carotid endarterectomy had an average 10-year CHD mortality of 19 percent. Since coronary mortality is typically 2 to 3 times that of major coronary events, this high mortality is indicative of a CHD risk equivalent. Similarly, in the ECST study (Barnett et al., 1998), symptomatic patients had very high death rates from nonstroke vascular disease, regardless of the percent of carotid artery stenosis at the outset. Finally, Norris et al. (1991) reported a much worse outcome in 696 persons with carotid bruits who were referred for Doppler studies for carotid stenosis. When persons had >75 percent carotid stenosis, rates of transient ischemic attacks (TIAs), stroke, and CHD events were very high (8.3 percent per year for CHD events), and were high even when stenosis was >50 percent. These studies taken together show that persons with symptomatic carotid artery disease are at high risk for major coronary events and so can be considered CHD risk equivalents.

Table II.12–2a. CHD incidence in Symptomatic Carotid Disease

Subjects	Disease severity (% Carotid Stenosis)	CHD deaths	Estimated 10-yr CHD risk
NASCET[†] Cohort of 1,415 patients randomized to carotid endarterectomy Mean age 66 33% current smokers	≥70% (n = 326) 50–69% (n = 858) <50% (n = 1368)	8 yr follow-up all-cause mortality: ≥70% 17% <70% 17% Most of deaths due to CHD	10-yr CHD death = 19%
ECST[‡] Entire cohort of 3,024 patients randomized to surgical vs. medical management Mean age 62 72% males 23% had Hx CAD 53% current smokers	0–19% (n = 140) 20–29% (n =279) 30–39% (n = 339) 40–49% (n = 312) 50–59% (n = 590) 60–69 (n = 369) 70–79% (n = 401) 80–89% (n = 410) 90–100% (n = 178)	All-cause mortality 6 yr follow-up was 27% for both treatment groups. All-cause mortality did not differ by % stenosis: 0–19% (24%) 20–29% (28%) 30–39% (28%) 40–49% (22%) 50–59% (27%) 60–69% (24%) 70–79% (28%) 80–89% (30%) 90–100% (31%)	Since 72% deaths were due to non-stroke vascular disease, 10-year CHD death is estimated at 30%
Norris et al., 1991 Persons with carotid bruits 327 men 369 women 235 had CHD Ages 45–90 Follow-up: 0.5–8 yr (mean 3.4 yr)		During follow-up, 132 CHD events occurred. CHD event rates were: 2.7%/yr for stenosis <50% 6.6%/yr for stenosis 50–75% 8.3%/yr for stenosis ≥75%	

[†] Ferguson et al., 1999

[‡] Barnett et al., 1998; Randomised trial . . . carotid stenosis 1998

Similarly, high CHD event rates have been documented in asymptomatic patients with advanced carotid artery stenosis. The natural history of this association is best illustrated by data from controlled clinical trials evaluating the effectiveness of carotid endarterectomy in these patients. When considering the CHD event or death rates reported for all subjects in the trials listed in Table II.12–2b, it is clear that patients with stenosis >50 percent, even if asymptomatic, have historically high CHD event rates thereby classifying them as a CHD risk equivalent.

Table II.12–2b. Asymptomatic Carotid Disease

Subjects	Disease severity	CHD events	Estimated 10-yr CHD risk
ACAS trial* Entire cohort of 1,662 patients randomized to carotid surgery or medical management; 69% Hx CHD 28% smokers 25% diabetics	Asymptomatic Stenosis ≥60%	2.7 yr follow-up: 84 deaths from MI (n =45) or other cardiac disease	10-yr MI mortality rate 10%; CHD mortality rate 19%
Veterans Affairs Cooperative Study Group† Entire cohort of 444 men Mean age 60 27% Hx MI 50% smokers 30% diabetics All received aspirin therapy	Asymptomatic Stenosis ≥50%	4 yr follow-up: 91 deaths from cardiac causes	10-yr CHD mortality rate 51%
Mayo Asymptomatic Carotid Endarterectomy Study‡ 158 patients 40% Hx CAD 15% diabetics	Asymptomatic Stenosis ≥50% Trial stopped due to high event rate in surgical arm secondary to cessation of medical therapy (aspirin)	2.5 yr follow-up: 12 CHD events	10-yr CHD event rate 30%
CASANOVA¥ 410 patients 42% Hx CAD 26% smokers 30% diabetics	Asymptomatic Stenosis ≥50%	3.5 yr follow-up: 50 deaths due to CHD	10-yr CHD mortality rate 35%

* Executive Committee for the Asymptomatic Carotid Atherosclerosis Study 1995

† Hobson et al., 1993

‡ Mayo Asymptomatic Carotid Endarterectomy Study Group 1992

¥ The CASANOVA Study Group 1991

Finally, other studies (Salonen and Salonen, 1991; Hodis et al., 1998; Chambless et al. 1997; O'Leary et al., 1999) have reported that carotid intimal-medial thickening of the carotid arteries in asymptomatic persons in whom carotid narrowing is <50 percent is still associated with increased risk for CHD. Although asymptomatic thickening of carotid arteries (<50 percent stenosis), in contrast to symptomatic disease and asymptomatic bruits of ≥50 percent stenosis, does not raise risk to the level of a CHD risk equivalent, these studies show that carotid artery atherosclerosis is accompanied by increased risk for new-onset CHD. Therefore measurements of carotid intimal-medial thickening represent an option for adjusting risk and therapies in persons with multiple risk factors (see Section II.5. Emerging Risk Factors).

3) Abdominal aortic aneurysm (AAA)

Limited data are available on the CHD risk in persons with atherosclerotic abdominal aortic aneurysm (AAA). The most complete study is that from Hertzer (1980) who reported the incidence of myocardial infarction following AAA resection in 343 persons followed 6–11 years postoperatively (Table II.12–3). The persons were separated into four groups according to pre-operative history of coronary disease. For persons with no evidence of previous CHD events, CHD mortality averaged 1.9 percent per year. Since the rate of CHD events is at least twice that of CHD mortality, even those without established CHD at time of operation would fall into the category of CHD risk equivalent. An even higher CHD death rate occurs in persons with prior CHD. This study thus supports the concept that AAA is a CHD risk equivalent.

Table II.12–3. Crude CHD Event Rate in Persons with Abdominal Aortic Aneurysm

Study population	N	Subsequent CHD mortality or event rate
Hertzer 1980 Persons operated on for abdominal aortic aneurysm (AAA) Persons separated into four groups based on preoperative CHD history and EKG Endpoint: incidence of fatal MI after surgical recovery: 6–11 yrs follow-up	300 men 43 women with AAA age 45–89y	On follow-up, 62 CHD deaths occurred among the 286 operative survivors. CHD mortality rates per year were: 1.9% in persons with no symptoms, no prior history of CHD, and normal ECG (31%) 2.0% in persons with no symptoms but previous MI by ECG (33%) 3.9% in persons with prior MI by history and ECG (23%) 3.9% in persons with angina/prior MI history but normal ECG (7%)

***Evidence statement**: Clinical forms of non-coronary atherosclerosis carry a risk for clinical CHD approximately equal to that of established CHD and hence constitute a CHD risk equivalent (C1). These conditions include peripheral arterial disease, carotid artery disease (transient ischemic attack or stroke of carotid origin, or >50% stenosis on angiography or ultrasound), and abdominal aortic aneurysm.*

Recommendation: *Persons with clinical forms of non-coronary atherosclerosis should have the same LDL-cholesterol goal (<100 mg/dL) as those for persons with established CHD and should be managed similarly (see Section IV.1).*

b. Diabetes as a CHD risk equivalent

Persons with type 1 or type 2 diabetes are at increased risk for CHD (Kannel and McGee, 1979a,b; Wingard and Barrett-Connor, 1995; Pyörälä et al., 1987). In women with diabetes, relative risk, but seemingly not absolute risk, exceeds that in men with diabetes (Pyörälä et al., 1987). Some of the increased CHD risk in persons with diabetes can be attributed to the major risk factors (Kannel and McGee, 1979a,b; Bierman 1992); other metabolic abnormalities, e.g., hyperglycemia and insulin resistance, probably contribute additional risk. Most literature relating diabetes to CHD risk considers type 2 diabetes, although cardiovascular complications are important for persons with type 1 diabetes as well. Because of the many differences between the two forms of diabetes, it seems appropriate to consider them separately.

Type 2 diabetes. This form of diabetes is characterized by insulin resistance, variable levels of endogenous insulin, and typically, by overweight/obesity and the metabolic syndrome. As hyperglycemia worsens, insulin therapy will become necessary. Persons with type 2 diabetes who are treated with insulin should not be confused with persons having type 1 diabetes who uniformly require insulin. Three lines of evidence support the concept that persons with type 2 diabetes from populations with high-average risk for CHD should be managed as if they have a CHD risk equivalent. But first it should be pointed out that hyperglycemia by itself does not raise risk to the level of a CHD risk equivalent. Instead, type 2 diabetes generally is accompanied by a constellation of metabolic risk factors that combine with hyperglycemia to impart a high risk. Furthermore, beyond having a high risk for first coronary events, persons with diabetes who develop CHD have a relatively poor prognosis for recurrent CHD events and coronary death. It is this constellation of factors rather than a single risk projection that justifies classifying most persons with type 2 diabetes in the United States as CHD risk equivalents. The evidence to support this recommendation will be reviewed.

First, several studies have shown that absolute risk for first major coronary events for persons with type 2 diabetes in high-risk populations approximates that for recurrent events in non-diabetic persons with clinical CHD. For example, in a Finnish population-based study, the seven-year incidence of myocardial infarction (fatal and nonfatal) among 1,373 non-diabetic subjects (ages 45–65 years) with and without prior myocardial infarction at baseline was 18.8 percent and 3.5 percent, respectively ($p<0.001$) (Haffner et al., 1998). In contrast, in 1,059 persons with type 2 diabetes, the seven-year incidence rates of myocardial infarction with and without prior myocardial infarction at baseline were 45.0 percent and 20.2 percent, respectively ($P<0.001$). The hazard ratio for CHD death for diabetic subjects without prior myocardial infarction as compared with non-diabetic subjects with prior myocardial infarction was not significantly different from 1.0 (hazard ratio, 1.4; 95 percent confidence interval, 0.7 to 2.6) after adjustment for age and sex, suggesting similar risk in the two groups. After further adjustment for total cholesterol, hypertension, and smoking, this hazard ratio remained close to 1.0 (hazard ratio, 1.2; 95 percent confidence interval, 0.6 to 2.4). Thus, in the Finnish population, which is known to be

a high-risk population, persons with type 2 diabetes without prior CHD have as high a risk for a myocardial infarction as do persons without diabetes with previous myocardial infarction.

Similar results were obtained from the recent OASIS study (Malmberg et al., 2000). In this study, persons with type 2 diabetes without CHD, average age 65, had rates of CHD events equal to that of persons with established CHD. Moreover, in the HOPE trial (Heart Outcomes Prevention . . . Investigators 2000a), persons with type 2 diabetes without prior cardiovascular disease, but with one or more cardiovascular risk factors, had an annual event rate for CHD of 2.5 percent. The results of these two trials further support the concept that persons with type 2 diabetes, even without clinical CHD, belong in the category of CHD risk equivalent.

In a major clinical trial, the United Kingdom Prospective Diabetes Study (UKPDS), the absolute 10 year risk for hard CHD was between 15 and 20 percent, depending on the subgroup (UK Prospective Diabetes Study [UKPDS] Group 1998a,c,d). Although this percentage was below 20 percent in some subgroups, it must be recognized that the persons in this trial had a diagnosis of diabetes made relatively recently; also, on average they were less obese than most persons with type 2 diabetes in the United States. In those with higher BMIs (>30 kg/m^2), 10-year risk exceeded 20 percent. Finally, it is well known that persons participating in clinical trials manifest a lower risk during the trial than does the population at large. Thus, UKPDS results are consistent with the concept that persons with type 2 diabetes belong in the category of CHD risk equivalent.

Since many persons develop type 2 diabetes after age 65, the question arises whether older persons with diabetes deserve the designation of CHD risk equivalent. Prospective studies (Kannel and McGee, 1979a,b) show that the relative risk for CHD for persons with diabetes versus without diabetes declines with age. Indeed, in a population-based study of older subjects with small numbers of diabetic subjects from Australia, the risk for CHD in non-diabetic subjects with preexisting CHD was greater than in diabetic subjects without preexisting CHD (Simmons and Simmons, 1998). Nonetheless, the combined risk factors of age plus diabetes appear to raise absolute risk for CHD to above 20 percent per decade.

Some persons with type 2 diabetes will not attain a 10-year risk for hard CHD of >20 percent when scored with algorithms from either Framingham (Wilson et al., 1998; Grundy et al., 1999c) or the International Task Force for Prevention of Cardiovascular Disease (Cullen et al., 1998). Such persons usually are younger and do not manifest multiple major risk factors. However, if their risk is projected to age 65, most of them will attain a risk of 20 percent. This high risk for premature CHD justifies more intensive risk reduction therapy earlier in life. On the other hand, in some populations where the baseline risk of coronary heart disease is very low, the presence of adult hyperglycemia weakly predicts CHD. One example includes persons of East Asian ancestry, e.g., China, Japan (Keys et al., 1984). In contrast, type 2 diabetes is accompanied by a very high risk for CHD in persons of South Asian origin.

A second reason for regarding persons with type 2 diabetes as having a CHD risk equivalent is that they have an increased case fatality rate with a myocardial infarction (Abbott et al., 1988; Herlitz et al., 1992; Miettinen et al., 1998). Prevention of myocardial infarction thus becomes a high priority. In one study (Miettinen et al., 1998), the one-year case fatality rate for a first myocardial infarction (from the onset of symptoms, including pre-hospitalization mortality) was

45 percent in men with diabetes and 39 percent in women with diabetes, compared to 38 percent and 25 percent for men and women without diabetes, respectively. Of the persons with diabetes who died, 50 percent of men and 25 percent of women died before hospitalization. Clearly, secondary prevention strategies are inadequate in these persons, and primary prevention is essential.

A third reason to aggressively prevent onset of CHD in persons with diabetes is that their overall prognosis for survival is much worse once they develop CHD than it is for CHD patients without diabetes (Haffner et al., 1998; Behar et al., 1997; Benderly et al., 1997; 1998; Karlson et al., 2000; Gustafsson et al., 2000; Thourani et al., 1999; Herlitz et al., 2000).

Classification of diabetes as a CHD risk equivalent in ATP III implies that enhanced benefit will be achieved from aggressive LDL-lowering therapy. Four studies have examined the benefits of cholesterol lowering with statins on CHD events in subgroups with diabetes (Pyörälä et al., 1997; Haffner et al., 1999b; Goldberg et al., 1998; The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group 1998; Downs et al., 1998) (see Table II.12–4). All of these studies have shown as much benefit in those with diabetes as in those without diabetes. The 4S, CARE, and LIPID studies were all secondary prevention trials. There were 202 subjects in the 4S with a clinical diagnosis of diabetes (Pyörälä et al., 1997). In this small group of subjects, simvastatin therapy was associated with a 55 percent reduction in major CHD (fatal and nonfatal CHD) ($p=0.002$) as compared with a 32 percent reduction in major CHD in non-diabetic subjects. In a further study of the 4S results (Haffner et al., 1999b) using the current American Diabetes Association criteria (fasting plasma glucose ≥126 mg/dL) an additional 281 diabetic subjects (without a previous diagnosis of diabetes) were identified. In this group simvastatin therapy was associated with a 42 percent reduction in major CHD ($p=0.001$). In the CARE study (Goldberg et al., 1998), 586 subjects with a clinical diagnosis of diabetes were identified. Pravastatin therapy reduced the risk for CHD (fatal plus non-fatal myocardial infarction, CABG and PTCA) by 25 percent in the diabetic group ($p=0.05$) as compared to 23 percent in the non-diabetic group ($p<0.001$). In the LIPID study (Long-Term Intervention . . . Study Group 1998), pravastatin reduced the incidence of fatal and nonfatal CHD by 19 percent in 792 diabetic subjects (p=ns) and 25 percent in the non-diabetic subjects ($p<0.001$). Although the reduction in CHD events in diabetic subjects was not significant with pravastatin, the test for heterogeneity in response between diabetic and non-diabetic subjects was not statistically significant. In AFCAPS/TexCAPS (Downs et al., 1998), a primary prevention study, only 155 subjects had a clinical diagnosis of diabetes. Among this small number of diabetic subjects, a 42 percent reduction in CHD was seen (p=ns) which was similar to the 37 percent reduction in CHD seen in the overall study population. Thus, in post-hoc analysis of all statin trials, there was a strong and consistent trend for benefit of LDL lowering in persons with diabetes.

Table II.12–4. CHD Prevention Trials with Statins in Diabetic Subjects: Subgroup Analysis

Study	Drug	No.	CHD Risk Reduction (Diabetes)	Baseline LDL-C mg/dL (mmol/L)	LDL-C Lowering	CHD Risk Reduction (Overall)	Ref
Primary Prevention							
AFCAPS/ TexCAPS	Lovastatin	239	-43%	150 (3.9)	-25%	-37%	Downs et al.
Secondary Prevention							
CARE	Pravastatin	586	-25% (P=0.05)	136 (3.6)	-28%	-23%	Goldberg et al.
4S	Simvastatin	202	-55% (P=0.002)	186 (4.8)	-36%	-32%	Pyörälä et al.
LIPID	Pravastatin	782	-19%	150* (3.9)	-25% *	-25%	LIPID
4S-Extended	Simvastatin	483	-42% (P=0.001)	186 (4.8)	-36%	-32%	Haffner et al.

* Values for whole group.

Downs et al., 1998; Goldberg et al., 1998; Pyörälä et al., 1997; The Long-Term Intervention . . . (LIPID) 1998; Haffner et al., 1999a.

With the growing prevalence of severe obesity and physical inactivity in the United States, type 2 diabetes has been observed to occur more frequently in young adults and even teenagers (Americn Diabetes Association 2000). It can be expected that early onset of type 2 diabetes will result in premature CHD. Clinical judgment is required to decide whether to manage these persons intensively with LDL-lowering drugs. LDL-lowering drugs need not always be started in young adults with type 2 diabetes. However, once LDL-cholesterol levels reach borderline high levels (130–159 mg/dL) or higher, LDL-lowering drugs become an option for reducing long-term risk. This is particularly so if other risk factors are present.

Persons with type 2 diabetes typically have atherogenic dyslipidemia, which represents a risk factor beyond elevated LDL cholesterol. This form of dyslipidemia in persons with diabetes is often called *diabetic dyslipidemia* which is described in detail in Section VII, Specific Dyslipidemia, along with recommendations for its management.

Type 1 diabetes. Although persons with type 1 diabetes are clearly at increased risk for CHD (Krolewski et al., 1987; Jensen et al., 1987), no study has specifically examined whether type 1 diabetic subjects have a risk of CHD as high as age- and sex-matched non-diabetic subjects with pre-existing CHD. This analysis is difficult to perform because persons with type 1 diabetes often develop diabetes at an early age. The intensity of LDL-lowering therapy therefore depends on clinical judgment. However, the ATP III panel favored starting LDL-lowering drug therapy in persons with type 1 diabetes when LDL-cholesterol levels are $\geq$130 mg/dL.

Evidence statements: *Persons with type 2 diabetes have a 10-year risk for major coronary events (myocardial infarction and CHD death) that approximates the risk in CHD patients without diabetes (A2, C1). This high risk can be explained by the combination of hyperglycemia plus lipid and nonlipid risk factors of the metabolic syndrome. In addition, persons with type 2 diabetes have a high incidence of death at time of acute myocardial infarction as well as a relatively poor prognosis for long-term survival after myocardial infarction (C1). Thus type 2 diabetes constitutes a CHD risk equivalent.*

Recommendations: *Persons with type 2 diabetes should be managed as a CHD risk equivalent. Treatment for LDL cholesterol should follow ATP III recommendations for persons with established CHD (see Section IV.1). For younger persons with type 2 diabetes, who otherwise are at lower risk, clinical judgment is required as to the intensity of LDL-lowering therapy. However, consideration should be given to using LDL-lowering drugs when LDL-cholesterol levels are ≥130 mg/dL.*

Evidence statements*: Persons with type 1 diabetes have increased risk for coronary heart disease. However, some persons with type 1 diabetes have a 10 year risk for CHD less than 15–20 percent (i.e., young persons without other risk factors [A2, C1]). Such persons will nevertheless have a high long-term risk for CHD (C1). Moreover, there is no reason to believe that the benefits of LDL reduction are different in persons with type 1 and type 2 diabetes (D1).*

Recommendations: *The intensity of LDL-lowering therapy in persons with type 1 diabetes should depend on clinical judgment. Recent-onset type 1 diabetes need not be designated a CHD risk equivalent; hence reduction of LDL cholesterol to <130 mg/dL is sufficient. With increasing duration of disease, a lower goal (<100 mg/dL) should be considered. Regardless of duration, LDL-lowering drugs should be considered in combination with lifestyle therapies when LDL-cholesterol levels are ≥130 mg/dL.*

c. High-risk persons with multiple risk factors

Many persons without clinical atherosclerotic disease or diabetes are still at high risk because of advanced coronary atherosclerosis. Those asymptomatic persons who have an absolute, 10-year risk as high as that of persons with established CHD, i.e., >20 percent, can be classified as having a *CHD risk equivalent.* When they are identified, it is appropriate to employ intensive risk-reduction therapy, similar to that used in persons with established CHD. The most reliable method currently available to identify these high-risk persons is assessment of absolute risk with Framingham risk scoring. Persons with CHD risk equivalents will be near the top of the risk spectrum, as determined by the presence of multiple risk factors.

Evidence statement: *Some persons with multiple CHD risk factors have an absolute 10-year risk for major coronary events (myocardial infarction and CHD death) of >20 percent (CHD risk equivalent) (C1).*

Recommendation: *For persons with CHD risk equivalents, the same recommendations should apply as for persons with established CHD (see Section IV.1).*

13. Models for clinical intervention: role of multidisciplinary team

Although epidemiology and clinical trials reveal the power of clinical intervention for both primary and secondary prevention, implementation of prevention guidelines has been less than optimal (Bowker et al., 1996; Pearson 2000). This deficiency is due in part to a structure of clinical management that is not designed for optimal preventive strategies. Successful prevention in clinical practice requires a multi-disciplinary team of health care professionals. The optimal organization of this team may well be a "lipid clinic" or "preventive cardiology clinic," but ATP III guidelines are designed so that primary care physicians can implement them in office practice.

Regardless of the clinical structure, implementation of ATP III guidelines is the responsibility not only of physicians, but also of registered dietitians and other qualified nutritionists, nurses, physician assistants, pharmacists, and other health professionals who must work together as a team in educating, treating, and following up each patient. There is consistent evidence from randomized trials demonstrating that approaches using a multidisciplinary team for the management of high serum cholesterol improve patient compliance, enlarge the scope of the population served, and improve the effectiveness of the guidelines (Becker et al., 1998; Blair et al., 1988; Debusk et al., 1994; Fonorow and Gawlinski, 2000; Hoogwerf et al., 1999a; LaBresh et al., 2000; Schectman et al., 1996; Shaffer and Wexler, 1995; Stuart-Shor et al., 1999; Thomas 1997; Urquhart 1995). There are an estimated 70,000 nutrition professionals (75 percent registered dietitians), 2.6 million registered nurses, and 190,000 pharmacists (80 percent in practice settings), and an increasing number of health educators. A team approach can be used to optimize education, monitoring, and follow-up. Physicians should identify a management strategy and work in concert with a health professional team to address the areas of diet, physical activity, and assistance with adherence enhancement. The multiple intervention strategies that can be employed when a multidisciplinary team approach is used offer persons optimal support for life-habit change. Finally, the success of ATP III's recommendations requires full participation of the patient, who must adopt and adhere to therapeutic modalities—whether life habit changes or drug therapy.

Evidence statement: *Use of a multidisciplinary team for management of high serum cholesterol improves patient compliance, enlarges the scope of the population served, and improves compliance to treatment guidelines (A2).*

Recommendation: *Physicians have a primary responsibility for implementing ATP III guidelines. In addition, a multidisciplinary team, potentially including nurses, dietitians, nurse practitioners, pharmacists, and health educators, should be utilized whenever possible.*

14. Cost-effectiveness issues

This section examines the issue of cost effectiveness of LDL-lowering therapy in the United States at the present time, and it considers changes that are likely to occur in the next few years. Costs and cost effectiveness of LDL-lowering therapy must be put into the context of the total costs of CHD and CVD. At present, direct medical costs for diagnosis and management of CVD in the United States exceed $100 billion annually. Similar amounts are lost in reduced productivity. Prevention of CHD with LDL-lowering therapy will reduce some of these costs. The most cost-effective approach to prevention of CHD is population intervention: diet modification, exercise, and weight control combined with smoking avoidance and cessation (Prosser et al., 2000). These approaches are safe, incur few direct costs, and offer benefits beyond CHD reduction. Clinical interventions to reduce LDL-cholesterol levels, the subject of ATP III, are less cost effective, but can be justified on other grounds in higher risk persons. The introduction of safe and effective LDL-lowering drugs makes clinical intervention attractive for higher risk persons. Nonetheless, the costs of drug therapy are the dominant factor determining cost-effectiveness of the clinical approach to cholesterol reduction.

Another major factor influencing cost-effectiveness of LDL-lowering therapy for individuals is absolute risk for CHD. Cost-effectiveness is greater for those at highest short-term risk and decreases progressively as risk of suffering a coronary event falls. Recently, clinical trials have revealed that LDL-lowering therapy will reduce relative risk for CHD at all absolute-risk levels. This fact heightens the importance of cost effectiveness analysis for selection of appropriate persons for clinical intervention. Whereas LDL-lowering therapy is efficacious to further reduce relative risk in lower risk persons, it is not necessarily cost effective by current standards.

a. Purpose of cost-effectiveness analysis of LDL-lowering therapy

Relative-risk reduction accompanying reduction of LDL levels at all levels of absolute risk opens the door to widespread use of LDL-lowering drugs. In fact, use of these drugs could easily rival that of drug therapy for hypertension in the United States. At present approximately 50 million Americans are candidates for antihypertensive drugs and approximately 25 million of these people are taking antihypertensive drugs (JNC VI 1997; Joint National Committee . . . 1997). The widespread use of LDL-lowering drugs, although potentially effective in reducing the burden of CHD in the United States, would be costly. The fundamental rationale for assessment of economic consequences of LDL-lowering drugs is the reality that resources are limited, whereas demand for medical therapies always exceeds available public resources. Consequently, difficult choices often must be made among potentially beneficial interventions. Resources are best allocated according to potential alternative uses. Evidence of efficacy and safety of drug therapy, a requirement for clinical intervention, is insufficient to make recommendations for drug use in a cost-constrained society. This is particularly true when many millions of persons are potential recipients of the therapy. Limited resources should be targeted to where they provide the greatest health benefits. One of the major objectives of cost-effectiveness analysis is to facilitate patient selection so that incremental benefits are greatest relative to incremental costs. Thus, for LDL-lowering therapy to be widely used in the U.S. population, it must be cost-effective by current standards.

Cost-effectiveness analysis of LDL-lowering therapy compares its incremental costs with alternative interventions and their incremental benefits. Assessment of cost-effectiveness is inherently relative, i.e., it requires comparison of costs and health outcomes among alternative interventions (including no intervention). The metric used is incremental cost-effectiveness, which is the additional cost required to attain an additional unit of benefit. The reason for assessing cost-effectiveness is not that a particular health benefit is not worth paying for in an absolute sense; instead, spending money for medical, health care, and other societal needs in other ways might benefit individuals or society more. Although intensive LDL-lowering therapy is attractive because it clearly reduces risk for CHD, cholesterol-lowering drugs are relatively expensive. For this reason, drug therapy is a prime subject for cost-effectiveness analysis, and for comparison with other accepted modalities of medical practice. For comparison, cost-effectiveness estimates of currently used diagnostics and therapies in medical practice are shown in Table II.14–1.

Table II.14–1. Cost Effectiveness of Common Diagnostic or Therapeutic Modalities*

Diagnostic or Therapeutic Modality	Cost Effectiveness Range† (dollars per year of life saved)
Antihypertensive therapy	$4,000 to $93,000
Screening mammography	$1,000 to $190,000
Renal dialysis	$20,000 to $79,000
Coronary artery by-pass surgery (left main disease/three-vessel disease)	$2,300 to $27,000
Exercise to prevent CHD	Cost-saving to $38,000
Aspirin to prevent CHD	Cost-saving to $5,000
Smoking cessation to prevent CHD	Cost-saving to $13,000

* Major source references:

Neumann et al., 2000; Stone et al., 2000; Tengs et al., 1995

Other references:

Barosi et al., 1997; Boer et al., 1999; Bulgin 1981; Buxton and West, 1975; Christie 1977; Churchill et al., 1984; Croghan et al., 1997; Cromwell et al., 1997; Cummings et al., 1989; de Koning et al., 1991; Douzdjian et al., 1998; Eccles et al., 1998; Eddy et al., 1988; Edelson et al., 1990; Fiscella and Franks, 1996; Gyrd-Hansen 1999; Harvald et al.,1983; Hatziandreu et al., 1988; Hlatky et al., 1997; Hristova, Hakama 1997; Johannesson et al., 1995; Johannesson et al., 1993; Johannesson et al., 1997b; Johannesson 1996; Johannesson 1994; Jones, Eaton 1994; Kerlikowske et al., 1999; Klarman et al., 1968; Knox 1988; Kodlin 1972; Kristein 1977; Krumholz et al., 1993; Lai et al., 1998; Leivo et al., 1999; Lindfors, Rosenquist 1995; Lindholm, Johannesson 1995; Littenberg et al., 1990; Ludbrook 1981; Mandelblatt et al., 1997; Marks et al., 1990; Meenan et al., 1998; Moskowitz, Fox 1979; Munro et al., 1997; Okubo et al., 1991; Oster et al., 1986; Pearson et al., 1976; Roberts et al., 1980; Rosenquist, Lindfors 1994; Salzmann et al., 1997; Secker-Walker et al., 1997; Shepard et al., 1995; Simon 1986; Simpson, Snyder 1991; Smith 1968; Sollano et al., 1998; Stange, Sumner 1978; Stason, Weinstein 1977; Streitz et al., 1998; Tsevat 1992; van der Maas et al., 1989; Warner et al., 1996; Wasley et al., 1997; Weinstein and Stason, 1982; Williams 1985.

† Rounded to closest thousands

b. Approaches to estimating cost-effectiveness of cholesterol-lowering therapies

Effectiveness analysis assesses net health benefit. For CHD prevention, effectiveness consists of extended survival, reduced morbidity, and enhanced quality of life. Effectiveness is generally expressed in terms of years of life gained or, preferably, quality adjusted years of life (QALY) gained. With the QALY measure, length of survival is weighted by the quality of survival.

Aspects of quality of life attributable to cholesterol reduction include improvements in functional status and reductions in the anxiety and disutility that accompany all CHD events.

Cost refers to net cost of health care resources consumed. LDL reduction includes the costs of physician services, counseling, tests for screening, case finding and monitoring, drugs, and the treatment of side effects. Subtracted from these costs are savings from reductions in medical care resources utilized to manage CHD sequelae. For LDL lowering, these cost offsets include savings from decreased hospital and ambulatory services for angina, myocardial infarction, revascularization procedures, stroke, and heart failure. Cost offsets also include savings from decreased economic losses secondary to increased gainful employment and productivity resulting from reduced CHD morbidity and mortality. The benefits of reducing LDL cholesterol are reflected in cost-effectiveness analyses in three ways: (1) Direct economic savings offset costs of LDL reduction, (2) avoidance of CHD mortality means a gain in survival, and (3) avoidance of the disability, distress, and pain from CHD counts as an increase in quality-adjusted life expectancy.

Several approaches to cost-effectiveness analysis of LDL lowering have been taken. Raw data for these analyses include estimates of risk based on Framingham risk scores and the results of clinical trials of cholesterol-lowering therapy in different population groups. Some investigators use sophisticated, complex, state-transition models to simulate the natural history of disease (Prosser et al., 2000). This approach attempts to incorporate and integrate data from the best available sources, including observational cohorts and health care administrative data in addition to clinical trials. Many factors are taken into account when developing the economic model (Table II.14–2). An alternate approach is to simplify the analyses to include only the essential factors (Caro et al., 1997). Here the major costs (e.g., drugs) are compared to savings from prevention of disease. Although the latter analysis does not include all the "hidden costs" of therapy, they show the "bare bones" cost-effectiveness of the simplest model for clinical intervention, namely, identification of the person at risk for CHD and initiation of life-time drug therapy without follow-up or monitoring. Of course, if the intervention algorithm of ATP III were to be followed rigorously, many of these factors shown in Table II.14–2 would have to be taken into account in the analysis. Nonetheless, in many cases, realities of clinical practice will constrain intervention over time towards the simplest model. These variations in actual practice account for some of the difficulties in making reliable estimates of cost effectiveness of LDL-lowering drugs.

Table II.14–2. Assumptions Used in Cost-Effectiveness Analyses of LDL-lowering Drugs*

- Efficacy of drug therapy
- Price of drugs (with or without wholesale discounts)
- Lag time between institution of therapy and first benefit (e.g., two years)
- Baseline risk of population
- Impact of individual risk factors on CHD risk
- Extrapolation of clinical trial results to the general population
- Prior dietary therapy before initiation of drug therapy (lessening cost effectiveness of drugs)
- Prior treatment with less expensive drugs (e.g., nicotinic acid) before starting more expensive drugs (e.g., statins) (lessening cost effectiveness of more expensive drugs)
- End points selected for cost-effectiveness analysis (e.g., morbidity reduction, life years gained, quality adjusted life years [QALY] gained)
- Projections of efficacy of secondary prevention measures (to extend life) after failure of primary prevention
- Coexisting primary and secondary prevention measures (e.g., aspirin prophylaxis)
- Quality of life adjustments
- Time discounting of benefits, risks and costs
- Methods adjustments for quality of life years
- Costs of treating new-onset CHD and sequelae
- Projected morbidity and mortality outcomes after onset of CHD
- Frequency and costs of physician visits for monitoring
- Adherence/compliance characteristics of population
- Thresholds for acceptable costs per year of life saved
- Country-specific costs

* Prosser et al., 2000

Cost-effectiveness analysis is complicated by variability in the health care delivery system, including drug prescription plans. Individuals with similar biological risk and clinical benefit face very different cost-effectiveness scenarios depending on resource prices, financial structure of medical plans, and subjective valuation of health resources. On the basis of the aggregate clinical experience of the clinicians on the panel, it was noted that, depending on the payment scheme, the annual costs of statin drugs can vary from $100 to $1000. This difference alone imparts an almost 10-fold difference in cost effectiveness for cholesterol-lowering therapy.

Beyond theoretical analyses, natural tensions exist at the level of the individual—both physician and patient. Health insurance programs seek to minimize payer costs, individuals desire to maximize their benefits relative to their health insurance and out-of-pocket payments, and physicians must make treatment decisions that optimize benefits to individuals without exceeding the bounds imposed by the insurance plan. In some cases, clinical judgment will push beyond payer controls; clinical treatment decisions must be individualized and guided by local

conditions and patient preferences. Moreover, cost-effectiveness constraints need to be reassessed as either clinical or economic data change.

c. Criteria for cost-effectiveness therapies

There are no explicit criteria for what is or is not cost-effective (Weinstein 1995; Tengs et al., 1995; Tengs and Wallace, 2000). Acceptable thresholds for cost-effectiveness are a reflection of available resources and cultural, social, political and individual values. The best situation occurs when an intervention both improves health and saves money. However, most commonly the costs of interventions that improve health outcomes are only partially offset by such savings. Empirically, the literature on cost-effectiveness indicates that most commonly accepted medical interventions in the United States have incremental cost per QALY gained below $50,000–$75,000 (Table II.14–1). Generally, interventions are considered highly cost-effective when the cost per QALY gained is below $20,000–$25,000, moderately high in cost-effectiveness when the cost per QALY is between $25,000–$50,000, borderline cost-effective when the cost per QALY is between $50,000–$100,000, and generally not cost-effective as the cost per QALY further increases. Clinical trial information on the impact of LDL lowering on functional status and quality of life is limited. Thus, it is difficult to directly weigh non-fatal outcomes and thereby assess cost per QALY. Economic analyses of persons with elevated cholesterol are further limited by restriction of measured resource use to a subset of cardiac services (most commonly revascularization procedures and CHD-related hospitalizations).

d. Cost effectiveness analysis for LDL lowering for secondary prevention (persons with established CHD)

Individuals with CHD are at high risk for subsequent major coronary events. They have a >2 percent annual risk for experiencing myocardial infarction or CHD death and approximately 4 percent annual risk for these events plus unstable angina and coronary revascularization. Cost effectiveness of secondary prevention has been estimated largely from the results of large, randomized clinical trials (Pedersen et al., 1996; Johannesson et al., 1997a; Glasziou et al., 1998; Ashraf et al., 1996; Grover et al., 1999; Tsevat et al., 2001). Among these trials, the very high risk of participants in the 4S trial made statin therapy highly cost effective (Pedersen et al., 1996). In the 4S placebo group, estimated 10-year risk for hard CHD events (myocardial infarction and CHD death) was about 36 percent. Several independent analyses applied to the trial as a whole indicated that costs per QALY average at current retail prices of drugs to be about $10,000 (Pedersen et al., 1996; Schwartz et al., 1997; Johannesson et al., 1997a; Grover et al., 1999; Prosser et al., 2000) Some investigators note nonetheless that even among persons with CHD, inherent risk for future CHD varies. Although cost-effectiveness analysis of subgroups of clinical trials is always problematic, ranges in cost-effectiveness have been reported, as exemplified by the recent analysis of the 4S trial by Prosser et al. (Table II.14–3). In two other secondary prevention trials (CARE, LIPID), 10-year risk for hard CHD was lower than that for the 4S trial, i.e., about 26 percent. It can be expected that cost-effectiveness analysis of these trials will reveal a higher cost per QALY gained than for the 4S trial (Goldman et al., 1999; Prosser et al., 2000). For example, in other trials of pravastatin therapy (PLAC I and PLAC II), one analysis (Muls et al., 1998) estimated costs per QALY saved in populations similar to that of CARE and LIPID to average about $25,000 at 1997–1998 drug prices. Also, Tsevat et al. (2001)

report for the CARE study that treatment with pravastatin increased quality-adjusted life expectancy at an incremental cost of $16,000 to $32,000 (average $24,000) per QALY gained. This value also is consistent with the variable cost-effectiveness within subgroups of persons with established CHD reported by Goldman et al., 1999 and Prosser et al., 2000.

Table II.14–3. Cost-Effectiveness Estimates of the 4S Trial by Gender and Age*

Costs ($) Per QALY Gained					
Group	**Age 35–44 y**	**Age 45–54 y**	**Age 55–64 y**	**Age 65–74 y**	**Age 75–84 y**
Men	4,500	1,800	3,900	6,700	9,900
Women	40,000	8,100	8,400	9,500	11,000

* Prosser et al., 2000

e. Cost effectiveness analysis in persons with CHD risk equivalents

Direct evidence of cost-effectiveness from randomized clinical trials is not available for persons with CHD risk equivalents. However, randomized trials and economic decision models consistently have confirmed that clinical benefit and cost-effectiveness are a function of population baseline risk. Models indicate that the cost-effectiveness of treating CHD risk equivalent populations is similar to that of those with symptomatic CHD (Glick et al., 1992; Goldman et al., 1999; Prosser et al., 2000). Thus, although the strength of evidence is somewhat less, cholesterol reduction in CHD risk equivalent populations is expected to exhibit the same degree of cost-effectiveness as observed in the clinical trials of secondary prevention.

f. Cost effectiveness of primary prevention

1) Cost effectiveness of dietary therapy for primary prevention

According to the analysis performed by Prosser et al. (2000), dietary therapy is more cost-effective than drug therapy for primary prevention. When the same assumptions are applied to dietary as to statin drug therapy, the costs per QALY gained usually are below $50,000 for persons with elevated LDL cholesterol and multiple risk factors. Prosser et al. (2000) also examined the cost-effectiveness of combining dietary therapy with an inexpensive drug (nicotinic acid). This combination enhanced the cost-effectiveness of therapy and eroded the incremental cost-effectiveness of statin therapy. A similar improvement in cost-effectiveness likely would result from combining dietary therapy with other therapeutic dietary options for LDL lowering (e.g., plant stanols/sterols and increased viscous fiber [see Section V]).

2) Cost effectiveness of drug therapy for short-term primary prevention

All interventions with drugs incur costs and have the potential for risk as well as benefit. Thus, evidence of demonstrated benefit is especially important before recommending primary prevention on a population basis, where individual benefits are reduced relative to secondary prevention. Primary prevention encompasses an extremely broad spectrum of CHD risk, and cost-effectiveness of drug therapy declines in direct relation to baseline population risk.

Evidence of the cost-effectiveness of drugs in primary prevention among people at moderate-to-high risk for CHD events is available from two sources: WOSCOPS and a series of economic decision models.

3) Cost-effectiveness for primary prevention based on WOSCOPS results

The West of Scotland Coronary Prevention Study (WOSCOPS) provides the best source of data from which to estimate cost effectiveness for primary prevention among individuals at higher risk for CHD events. As indicated by the event rate in the placebo group, WOSCOPS participants had an estimated 10-year risk for myocardial infarction and CHD death (hard CHD) of about 15 percent. A cost-effectiveness analysis was performed based on clinical resource use and costs observed in the WOSCOPS trial (Caro et al., 1997). As with the cost-effectiveness analyses of the other large statin trials, a Markov model was used to estimate the effects of alternative assumptions regarding long-term benefit of pravastatin therapy and a range of discount rates on expected number of people making the transition to symptomatic cardiovascular disease, survival, and recurrent coronary heart disease events for each treatment strategy beyond the trial period. Impact on quality of life was not estimated. Costs and benefits were discounted at 6 percent per year in the base case analysis. Incremental cost per year of life gained for the WOSCOPS cohort as a whole was estimated to be approximately $30,000 (UK costs and currency converted to dollars), ranging from approximately $19,000–$55,000, depending on assumptions used in various sensitivity analyses. These analyses incorporated only the initial management of CHD events; consideration of subsequent costs resulting from a CHD event would have resulted in somewhat improved estimates of cost-effectiveness. Based on analysis of the WOSCOPS trial, a reasonable estimate of costs per QALY saved at current retail drug prices of subjects with a 10-year risk of 15 percent would be about $50,000. A similar result was obtained by Morris (1997).

Estimates of cost-effectiveness from clinical trials in subgroups that are at variable risk are less reliable than for the whole cohort, but can be informative nonetheless. In WOSCOPS, restriction of statin therapy to the 25 percent of participants with a risk for hard CHD of >2 percent per year, who incurred 45 percent of all CHD events, revealed an incremental cost per additional year of life gained of approximately $20,000 (Caro et al., 1997; Shepherd 1998). This estimate clearly differs from that of the lowest-risk quartile of subjects, which had a risk for hard CHD of about 1 percent per year. A formal cost-effectiveness analysis has not been presented for this study population subgroup. However, extrapolation of the published WOSCOPS cost-effectiveness analysis to this subgroup yields an incremental cost per additional year of life gained of approximately $100,000, assuming statin therapy costs of about $1,000 per year.

4) Cost effectiveness of primary prevention based on the AFCAPS/TexCAPS trial

The AFCAPS/TexCAPS trial (Downs et al., 1998) studied the effectiveness of statins for risk reduction in participants with only borderline-high risk. Although statin therapy proved to be efficacious for reducing major coronary events, a comparison of AFCAPS/TexCAPS with other trials is hampered by the fact that the primary endpoint included unstable angina in addition to myocardial infarction and CHD death. Thus, the primary clinical endpoint differed from those of other trials in which major coronary events included only myocardial infarction and CHD death. In AFCAPS/TexCAPS, CHD rates in the placebo group were about 1.09 percent per year, with

unstable angina accounting for a significant half of all "major coronary events." From a purely economic point of view, differences between unstable angina and myocardial infarction are not substantial; costs incurred by hospitalization for unstable angina are similar in magnitude to those for myocardial infarction. However, total CHD events were incorporated into the WOSCOPS cost-effectiveness analysis described above rather than hard CHD only. Using WOSCOPS criteria for analysis, incremental cost per additional year of life gained would be >$100,000 for the whole cohort of AFCAPS/TexCAPS. For the higher risk subgroups, however, costs could be lower.

5) Cost-effectiveness in long-term primary prevention

Primary prevention aims to reduce risk for CHD in the long term as well as in the short term. The public health approach to long-term primary prevention generally is considered to have a favorable incremental cost-effectiveness ratio. However, at current retail drug prices, drug treatment for primary prevention in persons whose 10-year risk is <10 percent may not be considered cost effective, i.e., it would exceed $100,000 per QALY saved (Caro et al., 1997; Goldman et al., 1999; Prosser et al., 2000). Nonetheless, ATP III recommends consideration of drug therapy in lower risk persons (0–1 risk factor) whose LDL-cholesterol levels are very high (≥190 mg/dL) and in persons with multiple risk factors whose LDL-cholesterol concentrations are high (≥160 mg/dL); these recommendations include a trial of dietary therapy before drug consideration. The recommendation represents the attempt to achieve an appropriate balance between risk and costs. CHD is the foremost killer of Americans. Moreover, persons with elevated LDL cholesterol are at high long-term risk for CHD (see Table II.7–3 and Figure II.7–1). These facts must weigh against the costs of long-term drug therapy. In addition, the costs of drug therapy are difficult to judge. Many payment plans provide LDL-lowering drugs at prices below retail prices. Further, loss of patent protection and increased market competition likely will markedly reduce the prices of drugs over the long term. With each price reduction, cost effectiveness will increase. ATP III recommendations for long-term primary prevention reflect the considered judgment of the expert panel for the optimal management of persons with elevated LDL cholesterol. The recommendations attempt to balance benefit against costs, and it must be noted that several other approaches that were potentially beneficial but still more costly were rejected.

g. Summary

Cost-effectiveness is directly related to baseline population risk and inversely related to drug cost per unit of LDL lowering. As baseline risk increases and effective drug cost decreases, cholesterol lowering with statins becomes more cost effective. Cost-effectiveness also is a function of the time course of outcomes and costs. Cost-effectiveness becomes progressively more attractive as the overall risk of CHD events increases. Secondary prevention is clearly cost-effective, and almost always more cost-effective than primary prevention, except when the latter is applied to people whose risk of experiencing a first CHD event, e.g., diabetics, is equivalent to that of a recurrent event in those who already have clinical manifestations of CHD. Using common reference standard criteria, LDL lowering using statin therapy is very cost-effective for people with symptomatic CHD. Cost-effectiveness is similar for those with CHD risk comparable to that of people with prior CHD events (CHD risk equivalents). Cholesterol lowering certainly is cost-effective, and perhaps even cost saving, in the highest risk CHD

populations (diabetes mellitus with prior CHD events) and in high-risk populations with access to low acquisition cost drugs (as commonly negotiated by large managed care organizations and pharmacy benefit managers).

As baseline population risk declines, so does cost effectiveness. LDL lowering is cost-effective for primary prevention in higher-risk persons; at lower ranges of 10-year risk, it is not. Regardless, cost effectiveness is highly dependent on drug prices. This is illustrated by the projected progressive reduction of costs per QALY saved at each decrement in costs (Table II.14–4). Estimates shown in Table II.14–4 are based on cost-effectiveness analysis of recent clinical trials of LDL-lowering therapy described in the preceding discussion. They assume that costs per QALY gained are largely dependent on the costs of drugs. They also show an exponential rise in costs at lower absolute-risk levels as described by Hay et al. (1999).

Table II.14–4. Dependence of Cost Effectiveness on Costs of LDL-Lowering Drugs*

	Estimated Cost Effectiveness of LDL-Lowering Therapy (costs per QALY gained) at Different Costs of LDL-Lowering Drugs			
10-year risk†	$1000 per year	$500 per year	$250 per year	$125 per year
35%	10,000	5,000	2,500	1,250
25%	25,000	12,500	6,250	3, 125
15%	50,000	25,000	12,500	6,250
10%	100,000	50,000	25,000	12,500
5%	200,000	100,000	50,000	25,000

* Table developed from aggregate data available in existing literature (Pedersen et al., 1996; Johanneson et al., 1997; Glasziou et al., 1998; Ashraf et al., 1996; Grover et al., 1999; Tsevat et al., in Press; Schwartz et al., 1997; Prosser et al., 2000; Caro et al., 1997; Morris 1997; Hay et al., 1999)

† Risk expressed as 10-year risk for hard CHD (myocardial infarction + coronary death)

Specific ATP III guidelines for LDL-lowering therapy are influenced by cost-effectiveness analysis. However, they are made with the recognition that drug prices vary widely under different health care payment plans in the United States. In addition, it is noted that drug costs will likely decline in the future. For these reasons, guidelines for the American population cannot be as rigidly cost-dependent as in some other countries where there is a single-payment health care system and where costs of medication are relatively fixed and highly regulated.

Evidence statement: *At current retail drug prices, LDL-lowering drug therapy is highly cost effective in persons with established CHD (A1)*
Evidence statement: *LDL-lowering drug therapy is cost effective for primary prevention in persons with CHD risk equivalents (C1).*
Evidence statement: *At current retail drug prices, when 10-year risk for hard CHD (myocardial infarction + CHD death) is in the range of 10–20 percent per year, LDL-lowering drug therapy carries an acceptable cost-effectiveness (by current cost-effectiveness standards in the United States) (B1).*

Evidence statement: *At current retail drug prices, when 10-year risk for hard CHD (myocardial infarction + CHD death) is <10 percent per year, the cost-effectiveness of LDL-lowering drug therapy exceeds current cost-effectiveness standards in the United States (A2).*

Recommendation: *When 10-year risk for hard CHD is <10 percent per year, LDL-lowering drugs should be used judiciously. Priority should be given to dietary therapy, which is more cost effective. However, if LDL-cholesterol levels remain ≥160 mg/dL after dietary therapy in persons with 10-year risk <10 percent, LDL-lowering drugs should be considered if long-term risk for CHD is deemed to be high, i.e., if multiple major risk factors are present. When LDL-cholesterol levels are ≥190 mg/dL after dietary therapy, long-term risk is considered to be high regardless of other risk factors; thus LDL-lowering drugs should be considered. The need to reduce long-term risk in some circumstances can override the need to stay within currently acceptable cost-effectiveness criteria.*